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# CEREBRAL ARTERIES IN RELATION TO ARTERIOSCLEROSIS

C. R. TUTHILL, M.D.

BUFFALO

In a recent publication [1] I described the elastic layer in the cerebral vessels of twenty-three children who varied in age from birth to 15 years. The fatal illnesses of these children were the usual diseases of childhood with the exception of tuberculous meningitis, as this disease produces a well known endarteritis of the cerebral vessels. In all the patients examined, raised areas of split elastic fibers were found before and at the branching of large vessels and of many small ones. Intermingled with the split elastic tissue of these areas were long narrow nuclei and fibers, many of which stained yellow with van Gieson's method, while a few stained red. The split elastic fibers varied in number, but the type of splitting did not appear to depend on either age or disease. The areas differed from case to case in frequency and in location. At the bifurcation of the large vessels, they generally appeared as short, low mounds on one vessel wall. At the branching of the vessels they were raised and rounded over the opening, and extended along the walls of the main vessel and branch for varying distances. They were not found at all the branches or always at the same branching. They are apparently formed between the seventh intrauterine month and birth, since none were found in a 7 months' fetus.

Hackel [2] studied the elastic layer in the cerebral vessels of children, and also described the areas at the branching, but found no extensions until after the age of 20. He believed that age determined the frequency of the areas and the type of splitting of the elastic layer. Beneke [3] described similar areas in the bifurcation of meningeal arteries and attributed them to pulse force.

The present study continued the examination of the elastic tissue of the vessels of the circle of Willis and their branches, by means of longitudinally cut vessels in serial, paraffin and frozen sections. The number of patients was twenty-three; twelve were between the ages of 23 and 40, four between 40 and 50, two between 50 and 60, three between 60 and 70, one between 70 and 80 and one 83 years old. The

From the Pathological Department of Buffalo General Hospital.

1. Tuthill, C. R.: Arch. Neurol. & Psychiat. **26**:268, 1931.
2. Hackel, W. M.: Virchows Arch. f. path. Anat. **266**:630, 1928.
3. Beneke, R.: Virchows Arch. f. path. Anat. **287**:87, 1931.

vessels were grouped according to the changes in and arising from the areas of split elastic and collagen fibers at and before the branching of the vessels.

## RESULTS OF EXAMINATION

GROUP A.—*Areas of split elastic and collagen fibers at the branching of the large vessels similar to those found in childhood.*

The areas were generally found at the branching of many small and large vessels and along one vessel wall at the bifurcation of the large

Fig. 1.—Left and right anterior cerebral arteries with the anterior communicating artery showing areas of split elastic and collagen at the branchings, in a child aged 4 months.

vessels. The extensions before the branching and into the branched vessel were short, but differed slightly in length at each branching and in each case. The height and frequency of the areas were also not constant, but were essentially similar from case to case, and were therefore as in childhood. Such variations showed no dependence on advancing age, although the ages were 23, 28, 30, 32, 33, 35, 43 and 75. Fat was not demonstrable in any of the areas at the branching or in any part of the intima. Of the six patients below the age of 40, two died

of cerebellar tumor, two from accident, one from prolonged exposure to the sun and one of pneumonia. The blood pressures, when taken, were low. The past histories and observations at necropsy were without interest.

CASE 7.—A woman, aged 43, died of a cerebellar hemorrhage as the result of a blow on the forehead. She was known to have had diabetes for ten years previous to death. Past illnesses were sinusitis, scarlet fever, pneumonia and measles. The blood pressure was 180 systolic and 100 diastolic. At necropsy were found a few atheromatous plaques only in the aorta.

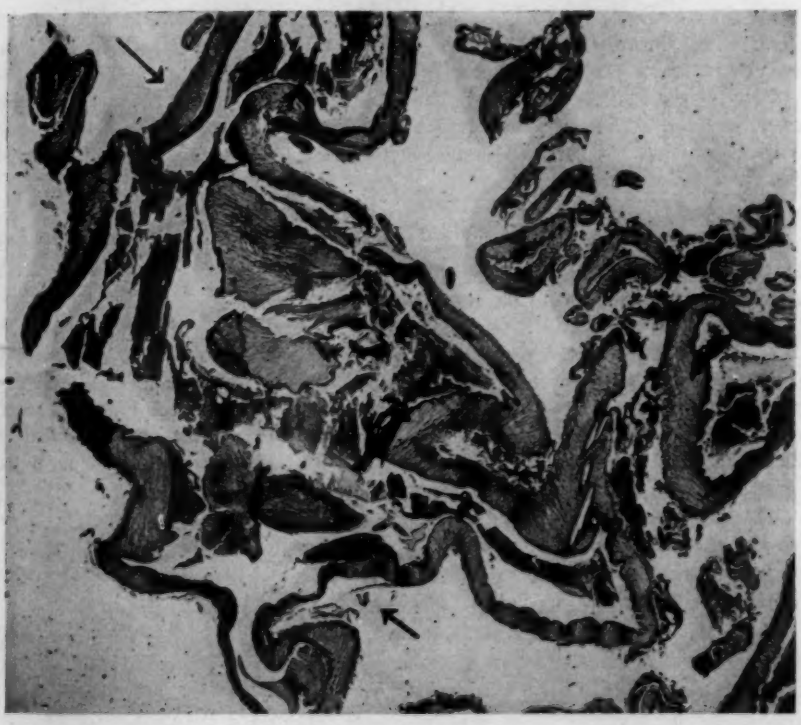

Fig. 2.—The left and right anterior cerebral arteries with the anterior communicating artery in a patient aged 32, showing similar areas of split elastic and collagen fibers at the branchings.

CASE 8.—A woman of 75 entered the hospital in the last stages of primary anemia. The blood pressure was 126 systolic and 66 diastolic. At necropsy were found arteriosclerotic, contracted kidneys and a few atheromatous plaques, only in the aorta.

GROUP B.—*Solitary and generalized moderate increase in the height and extension of the areas at the branching by a growth of lipoid-free collagen fibers and split elastic fibers.*

CASE 9.—A 23 year old girl fell in the street as she came from lunch and did not regain consciousness. At necropsy a rupture of the basilar artery was found

near the branching of the posterior cerebral and communicating arteries. The gross appearance of the cerebral and other arteries presented no abnormalities; the organs were also not remarkable.

Microscopic preparations of the site of the ruptured basilar artery showed no changes in the vessel walls. On the wall of the left middle cerebral artery was found a low extension of collagen fibers from the area at the branching of the middle cerebral and internal carotid arteries. These fibers persisted to the first branching of the middle cerebral artery. In the center of this extension was a small whirl of elastic tissue surrounded by thickly set oval nuclei. This was the only pathologic finding, as the areas at the branching of the other vessels were similar to those in group A.

CASE 10.—A man, aged 44, died of chronic tuberculosis of the lungs of two and a half years' duration. The blood pressure was 100 systolic and 65 diastolic. A few atheromatous plaques were present only in the aorta.

Low extensions of split elastic and collagen fibers from the areas at the branchings ran almost the entire length of the large cerebral vessels and of many of their branches. These extensions produced a slight increase in the number of areas at the branchings.

GROUP C.—*Slight increase in the height, frequency and extensions of the areas at the branching by split elastic and collagen fibers with absorption of fat in one or several areas.*

CASE 11.—A man, aged 67, suddenly fell unconscious in the street. At necropsy a large cherry-sized ruptured aneurysm was found at the site of the branching of the left middle cerebral and anterior cerebral arteries from the internal carotid artery. The cerebral vessels were thin and smooth except for one atheromatous plaque in the basilar artery. A few atheromatous plaques were present in the aorta and slight scarring in the kidneys.

In the microscopic examination, fat was demonstrable only as free lipoid in the aforementioned area at the branching of a small artery from the basilar artery. At a few branches the increased height of the areas and their short extension were formed of collagen fibers only.

CASE 12.—A man, aged 28, fell with a hemiplegia of the right side. The blood pressure was 120 systolic and 70 diastolic. Death occurred after several days. At necropsy a ruptured walnut-sized aneurysm was found at the first branching of the left middle cerebral artery with hemorrhage into, and destruction of, the surrounding brain tissue. No pathologic findings were apparent in any other vessel or organ of the body.

Fat cells were found between the split elastic and collagen fibers in the areas at several branches from the left middle cerebral and basilar arteries.

GROUP D.—*Slightly moderate increase in the height, frequency and extension of the areas at the branching by collagen fibers, fibroblasts and fat cells in simple formation or layered over split elastic and collagen fibers.*

At a few branchings the collagen fibers, fibroblasts and fat cells formed an inner layer to the areas of split elastic and collagen fibers,

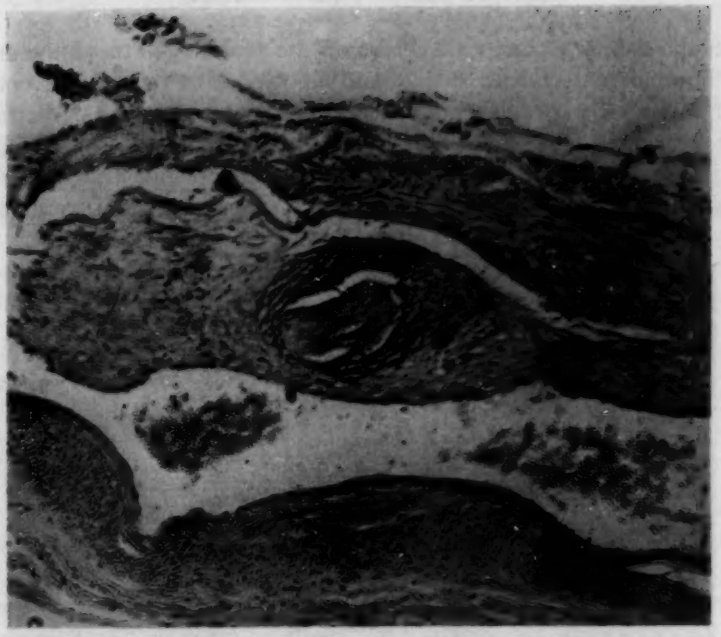

Fig. 3.—Unusual growth of collagen fibers around an elastic whirl—the only pathologic finding in all the cerebral vessels in a case of rupture of the basilar artery in a woman aged 23.

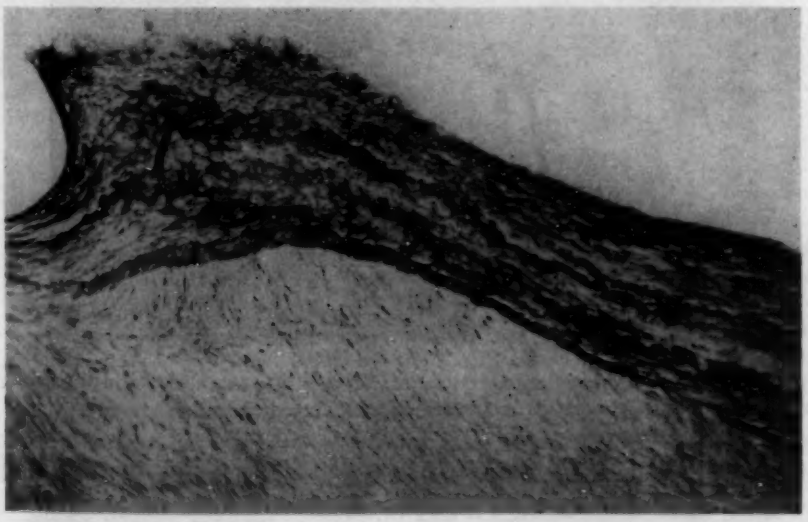

Fig. 4.—Early arteriosclerosis as shown by marked extensions of split elastic and collagen fibers from the areas at the branchings in a case of tuberculosis in a man aged 44. No absorption of fat was seen in any areas.

while at other branchings they formed the entire growth of the areas. The fibroblasts were both stellate and bipolar. The transition from the latter to fat cells was clearly shown. Lipoid was present as free fat in the outer part of the areas or in fat cells intermingled with the fibroblastic growth. Lipoid could not, however, be demonstrated in some areas of only collagen fibers. Extensions from the areas were found

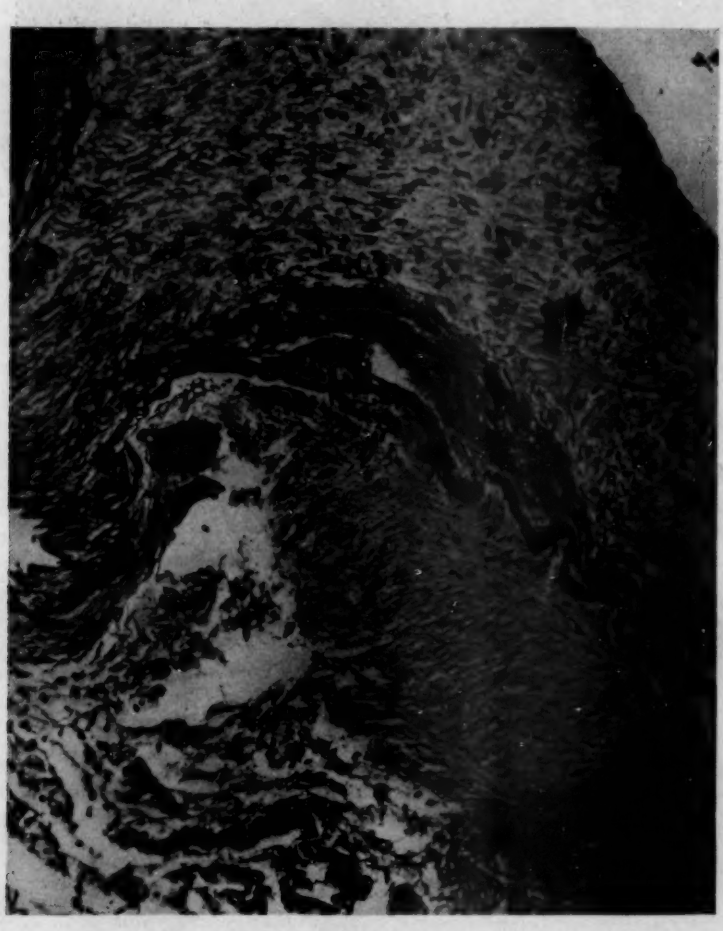

Fig. 5 (case 13).—Early arteriosclerosis as shown by an increase in the height and extension of the area at the branching by collagen fibers.

on only one side of the vessel wall. They were of varying length and composed of either collagen fibers or split elastic and collagen fibers. Fat cells were occasionally found between the fibers.

CASE 13.—A woman, aged 31, died in eclampsia. At necropsy no gross lesions were found in the vessels.

CASE 14.—A man, aged 30, died in uremia. He had a past history of scarlet fever, ten years of known hypertension and renal disease. During his final stay in the hospital the blood pressure varied from 212 systolic and 128 diastolic to 258 systolic and 132 diastolic. At necropsy there were found nephrosclerosis, marked atheromatosis of the aorta and an atheromatous area at the branching of the basilar and vertebral arteries.

CASE 15.—In a man, aged 68, who had always been healthy, pain in the chest developed with dyspnea and hemoptysis. The blood pressure was 112 systolic and 84 diastolic. Death occurred in twelve days. At necropsy were found pulmonary thrombosis, arteriosclerotic shrunken kidneys and slight atheromatous changes of the aorta and of the cerebral vessels.

In the microscopic examination one area at the branching of the middle cerebral artery showed no split elastic fibers, only cholesterol crystals, hyaline fibrosis and a few fibers of collagen as an inner layer. The other areas were similar to those in cases 13 and 14, while the extensions were formed of split elastic and collagen fibers without lipoid.

GROUP E.—*Moderate increase in the height, frequency and extension of the areas at the branching by fibroblasts, collagen fibers and fat cells, by collagen and split elastic fibers with few fat cells, or by hyalin in simple or layered formation with split elastic and collagen fibers.*

The extensions showed a marked increase in the height and a moderate increase in the length as compared with the previous groups. The extensions were chiefly on one side and along almost the entire length of the large vessels, but were not marked in the branches.

CASE 16.—A man of 39 had a history of a primary syphilitic infection at 36 years of age, with antisyphilitic treatment for three months. Two years later he complained of shooting pains in the legs and a girdle sensation. The colloidal gold curve was tabetic. Malarial treatment was given in the hospital, with definite improvement. A few months later the building in which the patient worked collapsed, and he fell unconscious from a blow on the head. The tabetic symptoms became greatly exaggerated, with marked difficulty in walking. He entered the hospital and died three weeks later from an ascending pyelonephritis. The blood pressure during the last year averaged 140 systolic and 65 diastolic; it was 60 systolic and 40 diastolic during malarial treatment and 150 systolic and 90 diastolic on the last admission. At necropsy only the aorta showed atheromatous plaques at the branching of the vessels.

Split elastic and collagen fibers were still present in a few areas at the branchings and extensions, but as an outer layer to a growth of collagen or of fibroblasts, fat cells and collagen fibers. In the other areas and extensions were bipolar and stellate fibroblasts and collagen fibers with numerous fat cells.

CASE 17.—A man, aged 42, with a history of no previous illnesses was brought to the hospital, partially disoriented from a fall in the street. The father and mother had both died of apoplexy. The blood pressure was 175 systolic and 20 diastolic. Death occurred in ten days from bronchopneumonia. At necropsy a small rupture was found in a cherry-sized aneurysm at the bifurcation of the left middle cerebral artery. The kidneys were not remarkable. Both the aorta and the cerebral vessels showed slight atherosclerosis.

Collagen fibers were the chief growth in both the extensions and the areas at the branching, forming either a single layer or an inner one to split elastic and collagen fibers. A few fine elastic fibers were occasionally found in the former collagen fibers. Small amounts of lipoid were demonstrable in a few areas and extensions as small globules in collagen fibers, in bipolar fibroblasts and in some transitional forms of the fibroblasts to fat cells. In only one area at the branching had free lipoid formed from broken-down fat cells. Several areas showed a marked growth of fibroblasts, fat cells and collagen fibers.

CASE 18.—A man, aged 83, died following a gastro-enterostomy for peptic ulcer. The past history was not remarkable. The blood pressure for many years

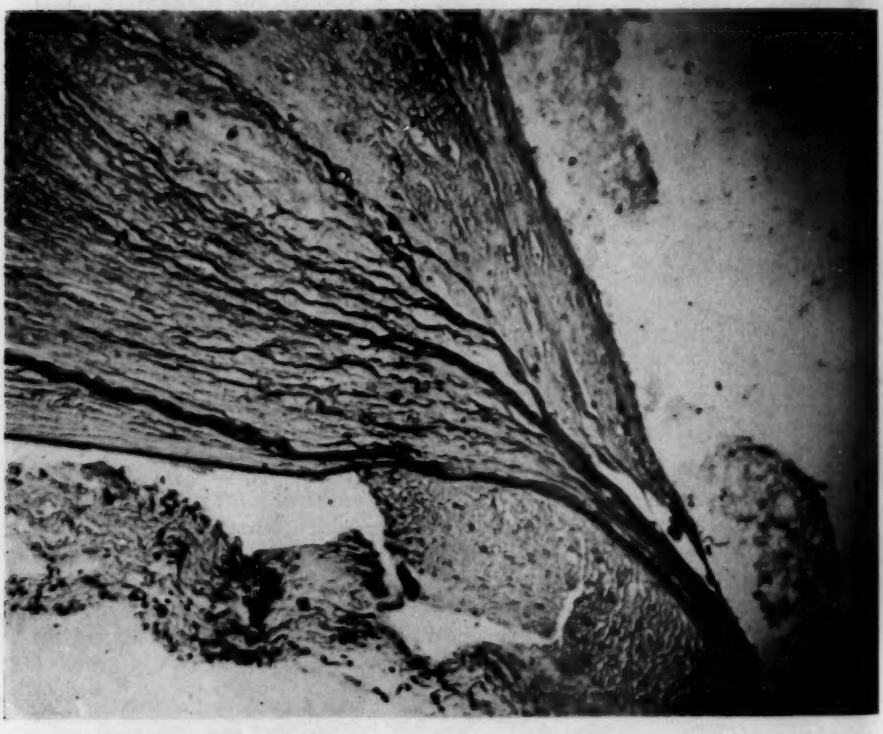

Fig. 6 (case 17).—Similar area of split elastic and collagen fibers increased in height by collagen fibers but with absorption of fat in both parts. The media is hidden by split elastic fibers at the branching of the vessel.

averaged 120 systolic and 70 diastolic with slight temporary rises. At necropsy were found arteriosclerotic contracted kidneys and marked atherosclerosis of all vessels. Near the branching of the right anterior communicating and right cerebral arteries was found a small bean-sized thrombosed aneurysm.

Split elastic and collagen fibers with a few fat cells were found at the branching of the anterior communicating and anterior cerebral arteries. All other areas were formed of hyalin, cholesterol crystals and a few inner collagen and split elastic fibers. A few extensions were composed of split elastic and collagen

fibers; the others were formed of hyalin and some inner collagen and elastic fibers. There were also some which showed a layered formation of split elastic and collagen fibers as an outer layer with hyalin as the inner layer.

GROUP F.—*Marked increase in the height, frequency and extension of the areas at the branching by a layered growth of collagen fibers over split elastic and collagen fibers with localized absorption of fat and hyalin.*

Fig. 7 (case 20).—Recurrence of arteriosclerosis as shown by an inner layer of collagen fibers over extensions of split elastic and collagen fibers. No absorption of fat occurred in either layer.

The extensions were high on both walls of the large vessels and in almost all the small branches.

CASE 19.—A man, aged 51, with a primary carcinoma of the lungs entered the hospital because of cough and swelling of the arms and hands. The blood pressure varied from 110 systolic and 80 diastolic to 115 systolic and 75 diastolic. Death occurred in a few weeks from bronchopneumonia. At necropsy metastatic carcinoma from the lungs was found in the brain. The kidneys and cerebral vessels were without gross pathologic changes. A few atheromatous plaques were present in the aorta.

The extensions and areas were either of split elastic and collagen fibers or of collagen, the latter joining the former. Hyalin was observed near one branching

as an outer layer to collagen fibers. In some areas a heavy growth of collagen formed an inner layer to split elastic and collagen fibers, while in neither layer was lipoid demonstrable. Few fat cells were found in any of the extensions or areas.

CASE 20.—A woman, aged 60, entered the hospital with an infection of the right middle ear of several weeks' duration. Past illnesses were typhoid fever, influenza, appendicitis, cystitis and two attacks of pneumonia. The infection of the middle ear became worse, and confusion, vomiting, dizziness, pain at the back of the neck and anuria developed. The blood pressure varied from 110 systolic and 60 diastolic to 130 systolic and 74 diastolic. At necropsy were found chronic otitis media, chronic osteomyelitis of the sphenoid bone, mild chronic meningitis, slight atheromatous changes of the aorta and acute glomerulonephritis. The cerebral arteries were smooth and thin.

The extensions were more marked than in case 19. Those of the larger vessels were in layered formation of split elastic and collagen fibers in the outer layer and collagen in the inner. Fat cells were occasionally observed between the fibers. A few fine elastic fibers were also found here and there in the collagen. In the small vessels were observed extensions of a moderately thick layer of split elastic and collagen fibers. A few areas at the branchings of the large vessels showed an inner layer of collagen and split elastic fibers and in their outer layers numerous fat cells, free lipoid, mitotic figures, small round nuclei with scanty protoplasm, spindle cells, cholesterol crystals and multinuclear cells. The other areas were continuous with the described extensions.

GROUP G.—*Marked increase in the height, frequency and extension of the areas in the large and small vessels by simple or layered growths in early or advanced regressive changes.*

CASE 21.—A man, aged 47, was admitted to the hospital because of the absence of knee jerks and optic atrophy. The blood pressure varied from 127 systolic and 76 diastolic to 144 systolic and 87 diastolic. There was no history of hypertension during the last three years of observation. The Wassermann reaction was negative. Death occurred suddenly. At necropsy were found small cysts of the kidneys, slight atheromatous changes of the aorta and marked atherosclerosis of the cerebral arteries. A walnut-sized thrombosed aneurysm was found at the branchings of the right internal carotid, middle cerebral, posterior communicating and anterior cerebral arteries.

In the microscopic examination of the large cerebral vessels high extension and high areas at the branching were indistinguishable in formation. Two-layered and three-layered growths predominated with a few extensions formed only of split elastic and collagen. The inner layer of the two-layered growth was formed of collagen with occasional fat cells. In some places of the outer layer there were split elastic and collagen fibers; in others, hyalin; in still others, fat cells, large cells with hemosiderin, free lipoid and spindle and multinuclear cells. The outer layer of the three-layered growth was chiefly hyalin, cholesterol crystals and calcium. The middle layer was of collagen fibers with a few fine elastic fibers, while collagen fibers only formed the inner layers. Fat cells were seldom observed in the middle or inner layers. In the small vessels were found moderately heavy extensions of split elastic and collagen fibers without lipoid. Dilated capillaries and a few light areas were observed in the media.

CASE 22.—A man, aged 52, fell in the street from a ruptured aneurysm of the basilar artery. The cerebral vessels were white, dilated and stiff. In the aorta were found syphilitic lesions.

The extensions and areas at the branchings of the large cerebral arteries were continuous, and were formed entirely of hyalin with calcium and occasional cholesterol crystals. The elastic layer was frequently absent, and no split elastic fibers were seen. Hemosiderin was demonstrable in a few cells in the outer part of the intimal growth. The capillaries of the media were dilated.

Fig. 8 (case 22).—Three-layered formation from two recurrences of arteriosclerosis. There is absorption of hyalin in the primary growth with an absence of collagen and split elastic fibers. Fine split elastic fibers are present in fat-free collagen fibers of the first recurrence. There is slight absorption of fat in the inner layer of collagen fibers of the second recurrence.

CASE 23.—A woman, aged 39, was depressed and became a secret drinker of alcohol two years prior to death. The drinking was abandoned during the last six months of life because of the onset of epileptic convulsions. The woman had never menstruated or developed secondary sexual characteristics. The uterus and adnexae were infantile. The blood pressure was increased during the last one and a half years and averaged 250 systolic and 110 diastolic. Three weeks before death a gradually increasing weakness occurred. At necropsy were found nephrosclerosis and marked atheromatous changes of the aorta and cerebral arteries.

Multiple hemorrhages, varying from the size of a pinpoint to 2 cm., were found throughout the brain. A hemorrhage the size of a hen's egg occupied almost the entire cerebellum. Other hemorrhages 2 cm. in diameter were found in the temporal and parietal cortex, putamen and pons.

All the large cerebral vessels showed high extensions of hyaline fibrosis, a few cholesterol crystals and calcium and an occasional split fiber of the elastic layer in the outer part. The smaller vessels showed varied lesions. In some of these vessels the lumen was almost occluded by split elastic and collagen fibers. In others were found clear fat cells projecting into the lumen, either alone or with a few elastic fibers pushed forward and distorted by fibroblasts and fat cells. The intima of the prearterioles of the meninges and of the brain showed split elastic and collagen fibers with or without fat cells. A few of the prearterioles were thrombosed with a hyaline change of the media and an aneurysmal widening in partial or complete rupture. Subendothelial hyalin was present in most of the arterioles of the brain substance.

Among all the cases in this series the media showed light areas beneath the intimal growth only in cases 11, 16 and 17. A hyaline change was not observed in the media.

## COMMENT

Aschoff [4] recently restated his theories of arteriosclerosis. He believes that there are two types, a presenile and a senile. The former occurs in nurslings because of a diet rich in cholesterol. In the senile type, there is first a physiologic fibrosis of the intima until the age of 40, and then a period of rest followed by fat absorption, fibrosis and absorption of hyalin and calcium. In the present series of cerebral vessels a fibrosis of the intima was not observed before the age of 40. Nor did the vessels of the six patients from 23 to 35 years of age in group A show an increase in the extension, height and frequency of the normal areas of split elastic and collagen fibers at the branching of vessels. There was a slight variation in the size of the areas in each case but not a gradual increase with age. Moreover, the areas did not show an increase with age when compared with their varied height and extension in childhood. They may even persist unchanged to the age of 75. This is contrary to the opinion of Ruehl [5] and Hackel [2] who believe that a hyperplasia of the elastic layer in the cerebral vessels develops with age. The extension of collagen fibers in case 9 might be considered a hyperplasia of age, but the unusual arrangement of cells around the elastic whirl suggests a localized reaction to loosened elastic tissue. It might also be suggested that the extensions of the areas of split elastic and collagen in case 10, in a man aged 44, were likewise a physiologic hyperplasia of the elastic layer. However, the patient in case 7 was 43 and showed a complete absence of such hyper-

4. Aschoff, L.: Beihefte z. med. Klin. **26**:1, 1930.
5. Ruehl, H.: Veröffentl. a. d. Kriegs- u. Konstitutionspath. **5**:21, 1929.

plasia. Furthermore, such an extensive growth of split elastic and collagen was not present in a patient aged 68, in whom fat had already been absorbed in one area at the branching. It must be considered, therefore, that any increase in the height, frequency and extension of the areas of split elastic and collagen fibers at the branching of the vessels is not of physiologic but of pathologic significance.

Ceelen [6] expressed the belief that a hyperplasia of the intima is the first change in arteriosclerosis and that the absorption of fat is secondary. On the other hand, Aschoff,[4] Anitschkow,[7] Hueck [8] and Jores [9] contended that arteriosclerosis is a disease of primary fat absorption. To support the latter theory it is necessary to show that an absorption of fat precedes an increase in the height and extensions of the areas at the branchings. Such a primary absorption of fat should therefore be evident in the vessels in group A and in those in the least advanced cases of arteriosclerosis. A primary absorption of fat could not be demonstrated. Lipoid was entirely absent from the vessels in group A. In the least advanced cases of arteriosclerosis were found free lipoid and fat cells in the areas at only a few branches in one case and in only one area of the other. Moreover, the fat-free areas at the remaining branches in these cases showed an increase in height and extension by a growth of split elastic and collagen or collagen fibers only. In the more advanced cases of arteriosclerosis were also found areas of split elastic and collagen increased in height by collagen in which was either no lipoid or but one or two fat cells. It may be argued, however, that such increases in height and extension of the areas at the branchings are the reaction to an early absorption of lipoid which has been reabsorbed. This does not appear to be probable, since lipoid-free areas of split elastic and collagen at the branchings are present in childhood. Furthermore, with the early absorption of fat in the areas, the split elastic fibers and collagen were spread apart and replaced by fat cells, while in the advanced cases the areas at the branchings no longer showed split elastic and collagen fibers, but only hyaline fibrosis, cholesterol or calcium. A destruction of split elastic and collagen was also apparent in the extensions of the areas. This was particularly demonstrated in the small vessels in case 23. In the split elastic and collagen fibers of these vessels were found numerous places in which large fat cells projected into the lumen either alone or with a few, distorted elastic fibers. The two-layered and three-layered extensions of the large vessels in

6. Ceelen, W.: Deutsche med. Wchnschr. **55**:1913, 1929.

7. Anitschkow, N.: Virchows Arch. f. path. Anat. **249**:73, 1924.

8. Hueck, W.: München. med. Wchnschr. **67**:535, 1920.

9. Jores, O.: Arterien, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2.

advanced cases were evidence of successive waves of arteriosclerosis and showed, therefore, all variations of the arteriosclerotic process from split elastic and collagen to only hyalin, cholesterol and calcium. It would seem, therefore, that in the cerebral vessels an increase in the height and extension of the areas at the branchings by split elastic and collagen or by collagen fibers precedes the absorption of fat and is the primary change of arteriosclerosis.

Since the earliest absorption of fat appeared to be in the collagen fibers and in the bipolar fibroblasts, the fibroblasts must develop from the collagen fibers. The disappearance of the collagen fibers either follows absorption of fat or is apparently due to the formation of fibroblasts and to the transition of the latter into fat cells which disintegrate and leave free lipoid. Such an absorption of fat prevents the formation of elastic fibers in a fresh growth of collagen. If, however, the absorption of fat in the latter is not immediate, split elastic fibers grow among the collagen fibers. A later absorption of fat may follow and destroy both types of fibers. There is no evidence that split elastic fibers develop after absorption of fat has destroyed the collagen fibers. Split elastic fibers are not found in the later regressive changes of hyalin and calcium, unless all the collagen fibers have not been destroyed. Split elastic fibers tend to follow the collagen fibers and are destroyed with them.

The onset and chronicity of arteriosclerosis appear to be varied. The extensions of the areas of split elastic and collagen fibers may be marked before fat is absorbed as in case 10 or slight as in the vessels in group C. There are apparently no areas of predilection at the branching in which fat is absorbed. The absorption of fat may occur in but one area as in cases 12 and 15. In the latter case, a complete hyaline change had taken place in this area before further fat was absorbed in other areas. On the other hand, the overgrowth of the areas at the branching by collagen and fibroblasts seems to denote a simultaneous hyperplasia and fat absorption and suggests, therefore, a rapid development of arteriosclerosis limited by death as in cases 13, 14 and 16. A moderately slow growth of arteriosclerosis would seem to have occurred when there is little absorption of fat, so that a penetration of the collagen by split elastic takes place as in case 17. Such moderately slow growth may be limited in extent but may recur as in case 19. The recurrences of arteriosclerosis may be wavelike with intermittances spreading through all the large and small vessels either slowly with little fat as in case 20 or with moderate absorption of fat as in case 16. In case 18 is demonstrated an almost total absence of recent new growth, while a second limited growth is almost completely hyalinized. A vigorous recurrence in only the small vessels is observed with marked fat absorption, thrombosis and rupture, while calcified lesions are present in the large vessels in case 23. The many small

hemorrhages and one large compact bleeding in the cerebellum in this last case do not confirm the belief of Boehne [10] who stated that such compact bleeding is not found with the small hemorrhagic areas of uremia and hypertension. Also the clear fat cells in the small vessels were similar to those found by Rothschild and Lowenberg,[11] although these authors did not consider their case one of arteriosclerosis.

The present series offers no consistent etiologic factor, either in the histologic examination or in the history. A primary lesion of the media was not observed, although it is the belief of Beitzke [12] that arteriosclerosis develops from changes in the media. In marked absorption of fat the intimal lesions appear to be of granulomatous formation, as is shown by the numerous mitotic figures, the large macrophages, the small round cells, the fat cells, cholesterol, free lipoid, bipolar fibroblasts and multinuclear cells. Also the change from lipoid to cholesterol, hyalin and calcium is similar to the calcification of fat granulomas. In syphilitic vessels were found the same regressive changes as in arteriosclerosis. This is contrary to the opinion of Jakob [13] who believed that both syphilis and arteriosclerosis might occur in the same vessel. Turnbull [14] thought that syphilis produced only local manifestations of arteriosclerosis, but in this case all the large vessels were similarly affected. It is not possible to determine the influence of syphilis on the vessels in the case of tabes. A toxicity from disturbed renal function might be considered in five cases. In only two cases was there a possible predisposition to arteriosclerosis shown by a family history of apoplexy.

The divergence of the ages in groups of similar lesions does not suggest that arteriosclerosis is a disease of old age but that it occurs at any time. In group C, the ages are 28 and 67; in group B, 23 and 44; in group D, 30, 31 and 68; in group E, 39, 42 and 83; in group F, 51 and 69, and in group G, containing the most severe cases, the ages are 47, 52 and 39.

The lesions of arteriosclerosis must be determined microscopically, since it is only the free lipoid or advanced regressive changes which are visible macroscopically.

Moschowitz [15] and Dietrich [16] believe that arteriosclerosis is due to the effect of intravascular pressure. Moschowitz cited as proof the

10. Boehne, C.: Beitr. z. path. Anat. u. z. allg. Path. **86**:566, 1932.
11. Rothschild, D., and Lowenberg, K.: Arch. Neurol. & Psychiat. **26**:993, 1931.
12. Beitzke, H.: Virchows Arch. f. path. Anat. **267**:116, 1928.
13. Jakob, A.: Spezielle Histopathologie des Grosshirns, in Aschaffenburg: Handbuch der Psychiatrie, Leipzig, Franz Deuticke, 1929, vol. 11.
14. Turnbull, H. M.: Quart. J. Med. **8**:201, 1915.
15. Moschowitz, E.: Virchows Arch. f. path. Anat. **283**:282, 1932.
16. Dietrich, K.: Virchows Arch. f. path. Anat. **275**:452, 1929.

development of arteriosclerosis in cases of increased pulmonary pressure, as in mitral stenosis. Steinberg [17] examined the pulmonary arteries of many patients and denied the influence of intravascular pressure in the production of pulmonary arteriosclerosis. Blood pressure was not an apparent cause of the vascular lesions in this series. In case 14 hypertension was of ten years' duration, but the marked fibroblastic growth indicated a recent onset. Hypertension was known to have been present for one and a half years in the last and most severe case, but there was also a family history of apoplexy, disturbed renal and endocrine functions and alcoholism.

The early experiments of Anitschow,[7] in which he was able to produce an absorption of fat in the intima of the aorta of rabbits by cholesterol feeding, suggested to many investigators a relation of diet and lipoid metabolism to arteriosclerosis. Raab [18] recently studied the diets of people in various parts of the world. He came to the conclusion that hypertension and arteriosclerosis are less frequent in countries in which the diet is low in animal fat and vitamin D content. Eskimos of Labrador are one of these groups. A relation of disturbed cholesterol metabolism to arteriosclerosis was also suggested by Aschoff [4] and Anitschkow.[7] The only patient with diabetes in my series showed no arteriosclerosis of the cerebral vessels, although diabetes was known to have been present for ten years, with a blood sugar content of 175 mg. and a blood pressure of 180 systolic and 100 diastolic.

Moreover, a relation of disturbed cholesterol metabolism to arteriosclerosis is not apparent in persons with xanthomatosis, in whom the blood cholesterol content is generally high. In the 26 year old patient of Chiari [19] the duration of the disease was eight years, but only a few yellow plaques were present in the aorta. Chester [20] recently reported a case in a man, aged 28, who showed no arteriosclerosis, although the disease was of eighteen months' duration. Arteriosclerosis was observed in two other patients with xanthomatosis by the same author.[21] In one patient, aged 44, there was also found degeneration of the posterior columns of the cord; in the other, aged 69, hypertension was present. Herzenberg [22] reported fat in the endothelium of the cerebral capillaries in a child with xanthomatosis. This fat was probably not in the endothelium but in the cells of the vessel walls as was observed by Ighenti.[23] In the reports of cases of Niemann-Pick disease, arteriosclerosis was not mentioned, although fat was demonstrable in the

17. Steinberg, U.: Beitr. z. path. Anat. u. allg. Path. **22**:307, 1927.
18. Raab, W.: Med. Klin. **28**:487, 1932.
19. Chiari, H.: Ergebn. d. allg. Path. u. path. Anat. **24**:316, 1931
20. Chester, W.: Virchows Arch. f. path. Anat. **279**:561, 1930-1931.
21. Chester, W., and Kugel, V. H.: Arch. Path. **14**:595, 1932.
22. Herzenberg, H.: Virchows Arch. f. path. Anat. **269**:614, 1928.
23. Ighenti, W. K.: Virchows Arch. f. path. Anat. **282**:585, 1931.

cells of the vessel walls. The absorption of hemosiderin in the intima in two cases of thrombosed aneurysms, is evidence that substances are taken up from the blood by intimal macrophages. The amount of hemosiderin was very small, although in one case the duration of the aneurysm was three years.

It is suggested that a relation of the volume of blood to the narrowing of the lumen of the vessel may exist. Also a mechanical influence may cause the growth of the areas of split elastic and collagen fibers at the branching of the vessels. It seems possible that the areas are developed to lead a sufficient quantity of blood from the main blood stream into the branches; therefore, as the volume of blood decreases the areas must enlarge. It would appear that the absorption of fat in the hyperplastic areas is similar to the absorption of fat in other hyperplastic growths, such as tumors. This conclusion is suggested from the observation that in only a few of the presented cases did absorption of fat occur in almost all parts of the intimal growth, and that these few cases were those of most rapid growth. Furthermore, the absence of a generalized absorption of fat and the presence of a localized fat absorption in the other cases do not offer proof of a theory of general metabolic disturbance as the cause of absorption of fat. Absorption of fat must therefore be due to localized changes in the hyperplastic intimal growth.

## CONCLUSIONS

At the branching of the large, and of many small, cerebral vessels are found areas of split elastic and collagen fibers which are present from birth and may remain unchanged through adult life. The onset of arteriosclerosis is an increase in the height and extension of these areas by collagen. Unless absorption of fat accompanies this growth of collagen, the areas are penetrated by split elastic fibers. The absorption of fat may be localized in only one hyperplastic area at the branching and in any part of such an area. Fat makes its first appearance in small globules in the fibers of collagen and in the bipolar fibroblasts. From the latter are produced fat cells. A granulomatous formation occurs in a marked absorption of fat and cholesterol. In any absorption of fat, the collagen fibers are destroyed and also the elastic fibers, if present. Free lipoid accumulates from the destruction of the fat cells, and this is followed by absorption of hyalin, cholesterol and calcium.

Arteriosclerosis may be rapid, slow or recurrent. Absorption of fat is marked in rapid growth and slight in slow growth. Recurrences may be of either rapid or slow growth and localized in the large or small vessels.

Hypertension, disease, diet, volume of blood, lipoid metabolism, disturbed renal function and syphilis were considered in relation to arte-

riosclerosis. Neither age nor the wear and tear of vessels are an etiologic factor.

Macroscopic examination discloses arteriosclerosis only when there are either advanced regressive changes or a large amount of free lipoid from broken-down fat cells.

Lesions of the media are apparently secondary to the changes in the intima.

It is suggested that the primary hyperplasia of the areas at the branching is dependent on the volume of blood and that absorption of fat occurs as in tumor formations.

# PNEUMONIA DUE TO FRIEDLÄNDER'S BACILLUS

CHARLES T. OLCOTT, M.D.
NEW YORK

Recent authors have confirmed Weichselbaum's [1] postulate that lobar pneumonia in a small percentage of cases is caused by Friedländer's bacilli in pure culture. The relatively frequent presence of members of the Bacillus mucosus-capsulatus group in the otherwise apparently normal upper respiratory tract [2] makes the finding of these organisms in sputum insufficient to establish them as the cause of pneumonia. Cases of pneumonia in which cultures of the blood or of the lung showed Friedländer's bacillus have been reported by Comba,[3] Béco,[4] Philippi,[5] Apelt,[6] Cole,[2d] Belk [7] and Sweany and his co-workers.[8] Fränkel,[9] Cole [2d] and Cecil, Baldwin and Larsen [10] noted the rarity of such cases, and the latter two gave the incidence as about four per thousand cases of pneumonia.

I found a pure growth of Friedländer's bacillus in cultures of the blood in five cases and in cultures of the lung in one case. These cases form the basis of this report. They were discovered among 204 consecutive autopsies, but there was no suggestion of an epidemic such as that reported by Zander.[11] In all six cases the course was acute, unlike that described by Letulle and Bezançon,[12] Westenmark and Berglund,[13]

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From the departments of pathology of New York Hospital and Cornell University Medical College.

1. Weichselbaum, A.: Med. Jahrb. **82**:483, 1886.

2. (*a*) Etienne, G.: Arch. de méd. expér. et d'anat. path. **7**:124, 1895. (*b*) Howard, W. T., Jr.: Philadelphia M. J. **1**:336, 1898. (*c*) Dunn, C. H., and Hammond, J.: Interstate M. J. **22**:1133, 1915. (*d*) Cole, R.: New York State J. Med. **19**:253, 1919.

3. Comba: Jahresb. ü. d. Fortschr. d. path. Microorg. **12**:101, 1896.

4. Béco, L.: Rev. de méd. **19**:385 and 461, 1899.

5. Philippi, E.: München. med. Wchnschr. **49**:1884, 1902.

6. Apelt, F.: München. med. Wchnschr. **55**:833, 1908.

7. Belk, W. P.: J. Infect. Dis. **38**:115, 1926.

8. Sweany, H. C.; Stadnichenko, A., and Henrichsen, K. J.: Arch. Int. Med. **47**:565, 1931.

9. Fränkel, A.: Ztschr. f. klin. Med. **10**:401, 1886.

10. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: Arch. Int. Med. **40**:253, 1927.

11. Zander, A.: Deutsche med. Wchnschr. **45**:1180, 1919.

12. Letulle, M., and Bezançon, F.: Ann. de méd. **12**:1, 1922.

13. Westenmark, N., and Berglund, N.: Acta radiol. **7**:626, 1926.

Brulé and his co-workers,[14] Collins and Kornblum,[15] and Sweany, Standnichenko and Henrichsen.[8] All occurred in men between the ages of 38 and 55. Two were Negroes, and four were white men. Three gave a history of alcoholism and three a history of chronic infections of the respiratory tract. The maximum duration of acute symptoms was ten days.

### BACTERIOLOGY

Friedländer's bacillus is identified by the hospital bacteriologist, Dr. George W. Wheeler, as a nonmotile, gram-negative bacillus with a large, easily stained capsule, which forms large, moist, semitranslucent, mucinous colonies when cultured on agar. It produces acid and gas in dextrose and usually in saccharose; it causes little or no fermentation of lactose; it does not produce indol; it gives rise to slight acidity in milk, without coagulation; it does not liquefy gelatin. The organism produces a rounded, mucinous surface growth.

### PATHOLOGIC ANATOMY

A lobular involvement has been described by Comba,[3] Stühlern,[16] the Mallorys,[17] Sisson and Thompson,[18] Westenmark and Berglund,[13] Belk[7] (one case), Brulé and his co-workers[14] and Collins and Kornblum.[15] On the other hand, Friedländer,[19] Béco,[4] Philippi,[5] Apelt,[6] Mosny and Pruvost,[20] Belk[7] (four cases) and Fremmel, Henrichsen and Sweany[21] have reported cases of lobar distribution. The diagnosis made at autopsy in four of the present series of cases was lobar pneumonia and in the fifth case, lobular pneumonia. In the sixth case, lobar pneumonia was shown in one lobe and lobular pneumonia in another.

Cross-section of the involved lobe in two cases showed a fairly uniform appearance, except that the periphery was grayer and the central

14. Brulé, M.; Huguenin, R., and Foulon, P.: Ann. d'anat. path. **4**:889, 1927. Brulé, M.; Huguenin, R., and Gilbert-Dreyfus: Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1370, 1927.

15. Collins, L. H., and Kornblum, K.: Arch. Int. Med. **43**:351, 1929.

16. Stühlern, V. R.: Centralbl. f. Bakt. (Abt. 1) **36**:493, 1904.

17. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914, p. 157. Mallory, T. R.: New England J. Med. **199**:196, 1928.

18. Sisson, W. R., and Thompson, C. B.: Am. J. M. Sc. **150**:713, 1915.

19. Friedländer, C.: Virchows Arch. f. path. Anat. **87**:319, 1882.

20. Mosny and Pruvost, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **35**:395, 1913.

21. Fremmel, F.; Henrichsen, K. J., and Sweany, H. C.: Ann. Int. Med. **5**:886, 1932.

parts of the lobe, hemorrhagic. Others [22] have reported this previously. The lobe was notably increased in density and consolidated, but showed some evidence that this consolidation represented a secondary confluence of previously separate areas of pneumonia. On section, large amounts of mucinous material oozed out as if the contents were under pressure, but the lobe in half of the cases showed also an indistinct granulation (Cordier [22b]).

A great majority of authors have noted destruction of the alveolar walls in pneumonia of this type [23] which may lead to necrosis or abscess formation,[24] but Lord [25] denied that this occurs. In my series there was beginning cavitation or abscess formation in cases 4 and 5; many of the septums in the lungs in other cases were notably edematous.

The number of organisms in the pulmonary vesicles is often enormous.[24b] The bacilli are both extracellular and intracellular. Fibrin is usually present in small amounts,[26] but figure 1 shows it traversing an interalveolar lacuna.[27]

A preponderance of polymorphonuclear cells has been noted in the pulmonary alveoli by many authors,[28] while others have found equal numbers of the two types [29] or mononuclear preponderance.[30] The duration of the disease and the blood count in my four cases with predominant mononuclears were as follows: Case 1, five days; 6,800 white blood cells, with 80 per cent polymorphonuclears, 16 per cent lymphocytes and 0 mononuclears. Case 2, eight days; 1,800 white blood cells, with 43 per cent polymorphonuclears, 33 per cent lymphocytes and 24 per cent mononuclears. Case 3, two days; 6,500 white blood cells, with 88 per cent polymorphonuclears, 10 per cent lymphocytes and 0 mononuclears. Case 6, three days; blood count not done.

In the other two cases, in which polymorphonuclears were predominant but many large mononuclears also present, the duration of the dis-

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22. (*a*) Smith, W. H.: J. Boston Soc. M. Sc. **2**:174, 1897-1898. (*b*) Cordier, V.; Badolle, A., and Brissaud, H.: Lyon méd. **118**:817, 1912. (*c*) Rosenkranz, K.: Thèse de Paris, 1912.

23. Thiroloix, M.: Bull. et mém. Soc. anat. de Paris **72**:152, 1897. Apelt.[6] Belk.[7] Stühlern.[16] Kornblum, K.: Pennsylvania M. J. **33**:312, 1930.

24. (*a*) Toenniessen, E.: München. med. Wchnschr. **58**:2608, 1911. (*b*) Lemierre, A., and Léon-Kindberg: Paris méd. **1**:67, 1925. (*c*) Belk.[7] (*d*) Sweany et al.[8] (*e*) Westenmark and Berglund.[13] (*f*) Mosny and Pruvost.[20]

25. Lord, F. T.: Disease of Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, 1925, p. 368.

26. Kokawa, I.: Deutsches Arch. f. klin. Med. **80**:39, 1904.

27. Miller, W. S.: J. Exper. Med. **42**:779, 1925.

28. Gouget, A., and Moreau, R.: Bull. et mém. Soc. méd. d. hôp. de Paris **34**:296, 1912. Sweany et al.[8] Mallory, F. B.[17]

29. Bensley, E. H.: Canad. M. A. J. **26**:681, 1932.

30. Brinckerhoff, W. D., and Thompson, R. L.: Rep. Boston City Hosp. **12**: 149, 1901. Belk.[7] Fremmel et al.[21]

ease and the blood count were as follows: Case 4, ten days; 4,400 white blood cells, with 83 per cent polymorphonuclears, 16 per cent lymphocytes and 1 per cent mononuclears. Case 5, from four to seven days; 13,000 white blood cells, with 89 per cent polymorphonuclears.

Figures 1, 2 and 4 illustrate the type of mononuclear cells found. Lord,[25] Lauche [31] and others expressed the belief that these intra-alveolar phagocytes represent desquamated epithelial cells; Gardner and Smith,[32] clasmatocytes, and Foot,[33] monocytes from the blood. The associated finding of many monocytes in the blood (e. g., in case 2) makes me lean toward the last explanation. As an indication that the leukopenia may be more than a terminal process, the similar changes in the blood in typhoid fever, also caused by a gram-negative bacillus, may be cited. When leukopenia and fairly numerous intra-alveolar monocytes are found in pneumococcic pneumonia, they usually occur later in the disease.

### REPORT OF CASES

CASE 1.—A white waiter, aged 38, had had nasal catarrh for years. There had been a chill, and there was a good deal of brownish, bloody sputum. There were signs of right lobar consolidation; the temperature was 104.2 F. Friedländer's bacilli was found in cultures of the sputum and blood, but there were no pneumococci. Death occurred on the fifth day of the disease.

At autopsy (two hours post mortem), cultures of the heart blood and sputum showed Friedländer's bacilli. Fibrinous plaques were seen on the pleura in the right axilla. The lungs were congested, the right weighing 1,625 Gm. and the left, 500 Gm. The right lower lobe was uniformly consolidated; its center was reddish and its periphery, gray. A block sank in water. Much mucinous material exuded on section, and there were fine granules on the cut surface which could not be scraped off on the knife. The spleen weighed only 100 Gm. The liver was large and fatty, weighing 1,400 Gm.

Microscopically, some of the alveoli of the right lower lobe were air-containing; others were not. The walls of many were injured, and the vessels congested. A few alveoli contained masses of fibrin (fig. 1). More of the intra-alveolar cells were mononuclear than polymorphonuclear, although clumps of the latter type were found. Short, thick, encapsulated bacilli were present in enormous numbers between the cells and in the mononuclear cells (fig. 2). No other organisms were found.

CASE 2.—A man, aged 55, a restaurant worker, with a history of alcoholism, had malaise and thoracic pain and raised blood-tinged to bloody sputum for a week before admission. The right lung showed signs of consolidation. The temperature was 103.6 F. Cultures of the blood and sputum showed Friedländer's bacilli. Death occurred seven hours after admission and eight days after the onset of symptoms.

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31. Lauche, A., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, p. 753.

32. Gardner, L. U., and Smith, D. T.: Am. J. Path. **3**:445, 1927.

33. Foot, N. C.: Am. J. Path. **3**:413, 1927.

Fig. 1 (case 1).—Section showing destruction of an alveolar wall with a mass of fibrin extending from one alveolus to the next. Gram-Weigert; × 180. The club-shaped mass in the right lower center represents the bulbous end of a torn alveolar septum. The innumerable small black spots represent extracellular and intracellular Friedländer's bacilli.

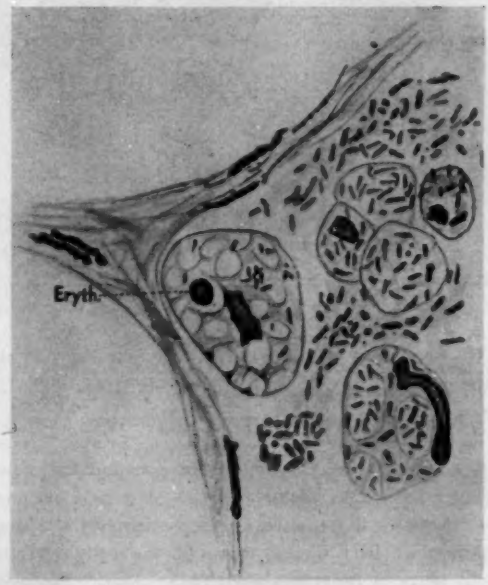


Fig. 2 (case 1).—A semidiagrammatic picture from a section of the lung showing a portion of an alveolar wall and mononuclear cells of various sizes. Gram-Weigert; × 500. A red blood cell (*Eryth.*) overlies one of them. The nuclei of the epithelial cells lining the alveoli are shown.

At autopsy (seven hours post mortem), the right pleura was opaque with some fibrinous exudate. The right lung weighed 1,360 Gm.; the left, 525 Gm. The right upper lobe was of greatly increased density. Section of the lobe (fig. 3) showed complete consolidation with some suggestion of fusion of smaller foci, the central portion being red, the peripheral part gray. No air-containing alveoli were recognized and a piece sank in water. The cut surface showed some fine granulations and much mucinous material. The other lobes were congested but aerated, and the bronchi were deeply injected.

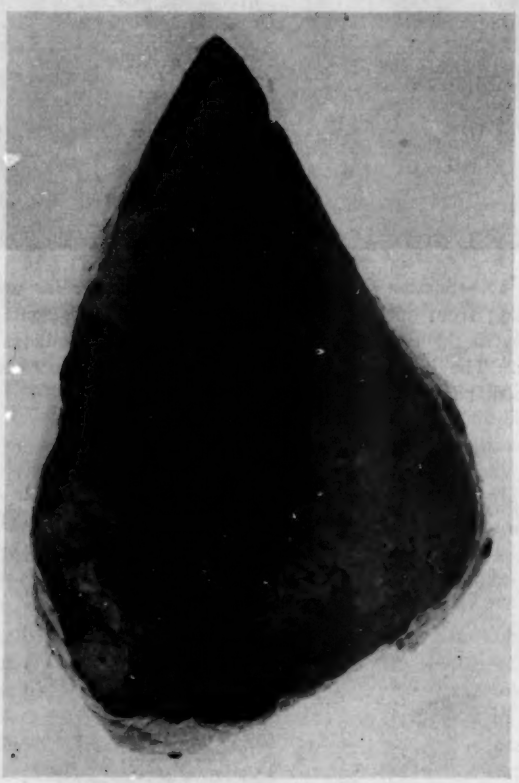

Fig. 3 (case 2).—Section of the lung two-thirds natural size showing complete consolidation of the entire lobe. The periphery is gray, and the central parts dark red.

Microscopically, some of the alveoli of the consolidated lobe (fig. 4) were opaque and somewhat translucent. Many vesicles showed a preponderance of large mononuclear cells, especially those with relatively few cells. Most of these were phagocytosing innumerable bacilli, and some of the cells were necrotic. Other alveoli showed small nests of polymorphonuclears. Many mucin-like strands were found around large numbers of encapsulated extracellular bacilli, but there was less fibrin than in case 1. Moderate destruction of the alveolar walls was present. No contaminating organisms were found in the sections. The bone marrow showed no significant histologic change.

CASE 3.—An unemployed white man of 44, a heavy drinker, without regular lodging or meals for several months, had pain in the left side of the chest, vomited and raised bloody, thin liquid sputum. There was dulness over the base of the left lung, with moist râles throughout both lungs and rigidity in both upper abdominal quadrants. The sputum showed Friedländer's bacilli and no pneumococci. Two blood cultures were negative. The patient died the day following admission, two days after the onset.

At autopsy (six hours post mortem), culture of the heart blood demonstrated Friedländer's bacilli. Old adhesions were found in both axillae. The right lung weighed 650 Gm.; the left, 1,300 Gm., and both were greatly congested. The pleural surfaces of the left were opaque. Most of the left upper lobe was consolidated. Cut sections revealed large amounts of hemorrhagic mucinous material,

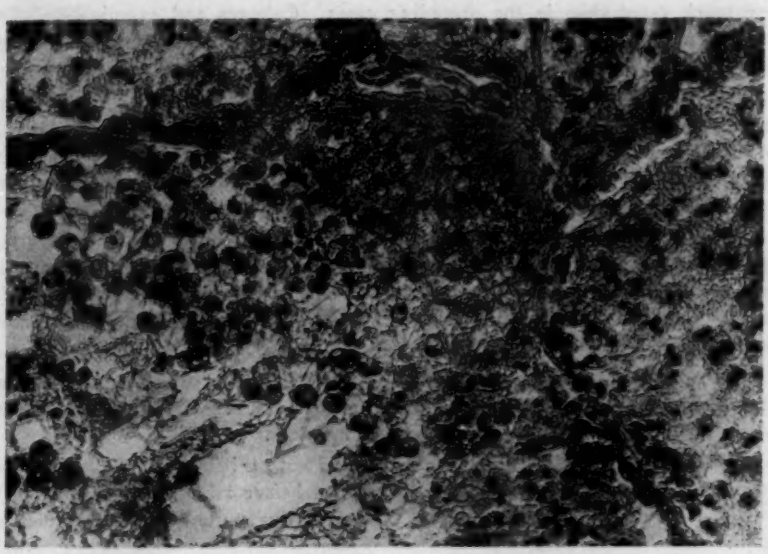

Fig. 4 (case 2).—The fine clear areas best seen at the bootom of the picture each represent an encapsulated bacillus; × 150. The preponderance of large mononuclear cells is clear. The fine strands represent mucinous material.

with some scarcely recognizable fine granulations. The left lower lobe contained many firm nodular masses, chiefly from 0.5 to 2 cm. in diameter, separated from one another by small areas of air-containing pulmonary tissue. The bronchi of all of the lobes were enormously congested and filled with thick, mucopurulent material. There was a large fatty liver weighing 3,150 Gm.

Microscopic sections from both areas showed pictures similar to those in cases 1 and 2, except that there were areas in which fused necrotic cells, largely mononuclears, presented a picture resembling that of influenza. Pigment-containing mononuclear cells were present in large numbers. No organisms other than those of Friedländer morphology were identified.

CASE 4.—This case is somewhat atypical. A West Indian Negro clerk, aged 47, had had signs of accessory nasal sinus infection for many years, chronic cough and dyspnea. Râles were found at both pulmonary bases, and mottling was seen

in the roentgenograms of both pulmonary fields. There were a large heart, a blood pressure of 220 systolic and 160 diastolic and signs of nephritis. The temperature was below 100.5 F. until the fifth day after admission and around 104 F. for the last four days. Death occurred ten days after admission, and four days after the significant elevation of the temperature.

Postmortem examination (four hours after death) gave a pure growth of Friedländer's bacilli from the left pleural and pericardial cavities, each of which contained 80 cc. of pus, and from the heart blood. Numerous small consolidated areas were found in the right lower lobe, and a cavity in the right upper lobe. The right lung weighed 450 Gm. and the cut surface and bronchi were congested. The heart weighed 750 Gm., with some fibrosis. The spleen weighed only 50 Gm.

Microscopic examination showed an irregular pneumonia with marked congestion. Polymorphonuclears predominated. Bacilli of Friedländer morphology were much rarer than in the preceding cases. Cultures and examination of the sections did not reveal any other organism, and the atypical picture was thought to represent a late process rather than one due to a secondary infection.

CASE 5.—A Negro longshoreman, aged 39, had had a "cold" for six days, with rusty sputum. There was dulness in the upper part of the right side of the chest, and a roentgenogram revealed a homogeneous shadow in this region. The highest temperature was 102 F.; it decreased somewhat. Cultures of the sputum and blood showed a pure growth of Friedländer's bacillus.

At autopsy (fifty hours post mortem), friable adhesions were found around the right upper and middle lobes. These lobes were adherent to one another and were firm. Cut surfaces were shiny, with numerous small abscesses on section. The bronchi were congested and contained mucinous material. Other lobes showed marked congestion. The right lung weighed 1,325 Gm.; the left, 425 Gm.

Microscopic examination indicated that the distribution was lobar and showed polymorphonuclear and mononuclear cells in the alveoli. There were some large gram-positive bacilli, obviously postmortem invaders.

CASE 6.—An unemployed Russian Jew of 52 with a history of alcoholism had a chronic cough which was worse for three days before admission. Culture of the blood showed no bacterial growth, but culture of the sputum showed Friedländer's bacilli.

Autopsy disclosed consolidation of the right upper and lower lobes with gross and microscopic findings as in cases 1 and 2. The right lung weighed 2,000 Gm.; the left, 500 Gm. Culture of the former gave Friedländer's bacilli.

## SUMMARY

Five cases of pneumonia in which the blood at autopsy contained Friedländer's bacilli and a case in which positive cultures were obtained from the lung post mortem are reported. In all the course was acute, death occurring in from two to ten days after the onset of acute symptoms. All of the patients were men between 38 and 55 years of age; four were white and two were colored. Three had a definite history of alcoholism and three a history of chronic infections of the upper respiratory tract. In four of the cases blood counts gave less than 7,000 leukocytes; in one of these less than 2,000, with 24 per cent large mononuclears.

In four of the cases there was pneumonia of lobar distribution; in one, pneumonia of the lobular type, and in one lobar distribution in one lobe and lobular in another. In five cases, a typically mucinous appearance was seen on cross-section. The pulmonary alveolar walls were more or less injured in all.

Sections of four of the lungs (cases 1, 2, 3 and 6) showed enormous numbers of bacilli in the pulmonary alveoli, while fewer bacilli were found in the other two. Large mononuclear cells in great numbers were the predominating intra-alveolar cell in these four cases, with polymorphonuclears in lesser numbers. The proportions were reversed in the other two cases. The mononuclear cells are believed to be monocytes.

# RHABDOMYOMA OF THE UTERUS

WARREN G. HARDING, II, M.D.
AND
FRANKLYN D. HANKINS, M.D.
LOS ANGELES

## INTRODUCTION

The term "rhabdomyoma" refers to tumors which present the histologic picture of striated muscle. It is not necessary to assume that the structure is identical with that seen in adult voluntary muscle, but the histology must represent a stage in the histogenesis of striated muscle. The tumors may be either benign or malignant. As with most other tumors, the degree of anaplasia corresponds relatively to the rapidity of the growth. Dewey [1] classified these growths into (1) those arising in preexisting striated muscle and (2) those arising in tissue which normally contains no striated muscle. She thought that the growths belonging in group 2 were teratomatous. The etiology of rhabdomyomas, regardless of their point of origin, remains veiled in the obscurity surrounding the causal factors of practically all malignant tumors.

The occurrence of this type of neoplasm is infrequent. In reviewing approximately eighteen thousand necropsies performed at the Philadelphia General Hospital, Cohen [2] reported one case of rhabdomyosarcoma, which presented generalized metastases. The bulk of the tumor was found in the region of the right kidney. Cohen's reasons for preferring the term "rhabdomyosarcoma" to "rhabdomyoma" are not given. In the last nine thousand consecutive autopsies performed at the Los Angeles County General Hospital we have found only one tumor of this type. In more than thirty thousand surgical specimens examined in this hospital, no tumor consisting of striated muscle has been found.

## REVIEW OF THE LITERATURE

In the literature prior to 1903, sixty-three cases of rhabdomyoma were described. Benenati [3] divided them into (1) rhabdomyomas arising in the urogenital system and (2) those arising elsewhere. There were thirty-nine cases in group 1, of which six were considered to

From the Department of Pathology, Dr. Newton Evans, director, Los Angeles County General Hospital, unit 1.

1. Dewey, K. W.: Arch. Path. **3**:645, 1927.
2. Cohen, J. S.: Arch. Path. **13**:857, 1932.
3. Benenati, Ugo: Virchows Arch. f. path. Anat. **171**:418, 1903.

be primary in the uterus. In 1928, Bonnard [4] described a pedunculated rhabdomyoma occurring in the uterus. The growth was firm, glistening and multilobular, and had extended through the walls of the uterus and had surrounded the ovaries and tubes. Ewing [5] stated that tumors of this type occur in the uterus almost exclusively as sarcoma botryoides, Pfannenstiel.

Many theories have been advanced to explain the pathogenesis of neoplasms of this type. For practical purposes, the theories may be classified roughly into three main groups: 1. The growth represents a metaplasia of preexisting smooth muscle cells either in the uterus or from the walls of the arteries found within the organ. 2. It represents a metaplasia originating in the fibrous tissue of the organ. 3. It is a product of the ungoverned growth of misplaced embryonic cells. This last group is based largely on the Cohnheim cell rest or cell inclusion theory for tumors in general. Benenati [3] supported the latter explanation by ascribing the formation of the tumor to misplaced blastomeres, basing his opinion on the fact that a large proportion of the growths are found in the urogenital system, the embryologic development of which is complex and intimately related to the development of the muscles of the trunk. Shattock [6] stated that there are normally many striated muscle fibers surrounding the trigon of the bladder in the fetus, and that vagrant sarcoblasts from this region furnish the point of origin for the tumor. In a study of rhabdomyoma occurring in the uvula, Nicory [7] agrees with those who advance the cell inclusion theory, but suggests that in certain cases an injury to preexisting striated muscle cells might set up an embryonic proliferation leading to the formation of a rapidly growing muscle tumor. Wolbach [8] apparently held that the tumor arises from embryonic muscle cells; he traced its histogenesis through the following processes of differentiation: The myoblast, or embryonic muscle cell, at first a round or ovoid cell, becomes polyhedral and later fusiform. It contains clusters of paired centrioles located in the perinuclear zone. The centrioles go through a process of multiplication, and the clusters and the individual centrioles disperse. Fine fibrils appear connecting the dispersed centrioles which form the striations seen in the adult type of tissue. Accepting this explanation, Derman and Golbert [9] felt that the so-called sarcomatous

4. Bonnard, A.: Bull. Assoc. franç. p. l'étude du cancer **17**:110, 1928.

5. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 237.

6. Shattock, S. G.: Proc. Roy. Soc. Med. **3**:31, 1910.

7. Nicory, C.: Brit. J. Surg. **11**:218, 1923.

8. Wolbach, S. B.: Anat. Rec. **37**:255, 1928.

9. Derman, G. L., and Golbert, Z. W.: Virchows Arch. f. path. Anat. **282**: 122, 1931.

or syncytial portions of the tumor represent stages in the normal development of striated muscle.

## REPORT OF CASE

*History.*—A Negro girl, aged 3 years, was first seen when admitted to the hospital on Oct. 4, 1931, with a history of a foul-smelling vaginal discharge of two weeks' duration. The discharge was clear and yellow at the onset, but one week later it became bloody. The patient's appetite became poor, and a mild fever appeared during the second week of the illness.

A hemorrhagic, necrotic, sloughing tumor was present in the vagina. There was a mild secondary anemia. The urine contained a trace of albumin and many bacteria. There was no ulceration or recognizable tumor in the wall of the bladder, although the right ureteral orifice could not be located and mild cystitis was present.

On exploratory operation one week later, a necrotic tumor mass filling the anterior portion of the pelvis was found. It was extraperitoneal, the bulk lying between the bladder and the uterus and extending into the broad ligaments. A specimen was taken for biopsy, and the condition was reported as embryonal tumor.

The patient was given high voltage roentgen therapy. The recovery from the exploratory operation was uneventful. She was apparently comfortable for three weeks, although the vaginal discharge persisted. At this time frequent urination developed.

The patient reentered the hospital on November 3, following the sudden onset of anuria on the preceding day. She had a fever of 101 F. (rectal), a pulse rate of 140 and a respiratory rate of 56. There was slight edema about the eyes. The abdomen was distended, and a large, firm, irregular mass extended to the region of the umbilicus. The abdomen above the mass was tympanitic. The vagina was filled with hemorrhagic, necrotic tissue. The anemia had increased, and the urine showed a marked increase in albumin.

During the ensuing six days the child was catheterized every eight hours. She became progressively drowsier and complained of severe abdominal pain. On November 9, she expired suddenly, with evidence of pulmonary edema.

*Postmortem Examination.*—The examination was limited to the abdomen. A firm, nodular tumor was found, which apparently arose in the anterior wall of the uterus below the uterovesical fold. The bladder was located on the upper anterior surface of the tumor and contained about 50 cc. of clear urine. The growth had infiltrated the trigon. The ureteral orifice on the left was found to lie in the tip of a polypoid mass of the neoplastic tissue. The orifice of the right ureter was not involved. Both ureters, however, were compressed as they passed through the surrounding tumor tissue and were dilated above the point of obstruction. The growth had permeated both broad ligaments in their entire extent. The entire uterus was replaced by neoplastic tissue, and the canal was distended by a necrotic, polypoid mass which had pushed through the cervix. The cut surface showed that the entire tumor was composed of firm white lobulated tissue with scattered yellow, granular striations resembling, in the gross, the ordinary fibromyoma. No metastatic deposits were found in the lymph nodes draining the pelvis or in the liver.

*Microscopic Examination.*—The tissue from the tumor was fixed in 10 per cent formaldehyde. Various stains, including hematoxylin and eosin, phosphotungstic

acid-hematoxylin, Mallory's and van Gieson's connective tissue stains, and Perdrau's method were tried.

The microscopic structure permitted the growth to be divided into two portions. The greater portion consisted of a well differentiated tissue resembling adult striated muscle and a less extensive portion composed of anaplastic tissue resembling fibrosarcoma. The resemblance of the embryonic tissue to fibrosarcoma, however, was only superficial, as was clearly shown after more minute examination.

The characteristic portions of the tumor when stained with hematoxylin and eosin revealed elongated cells having an acidophilic, very finely granular cytoplasm

Fig. 1.—Photomicrograph of the differentiated portion of the tumor showing the abundant fibrous connective tissue stroma. Hematoxylin and eosin stain; × 80.

which contained definite cross-striations. The presence of longitudinal striations was suggested in an occasional cell. Minute study of the isotropic bands did not reveal the presence of Krause's membrane. The fibers were irregularly arranged and showed no tendency to form primary muscle bundles. The sarcolemma was apparently branched at the extremities of the fibers. The nuclei were large, hyperchromatic and centrally located; they were piled up in groups of from six to eight in one cell and showed a tendency to be rounded. Mitotic figures were rarely seen in these areas. The nucleoli numbered from one to three and were usually found immediately beneath the nuclear membrane. The surrounding collagenic fibrous tissue as demonstrated by van Gieson's stain was abundant, loosely packed and moderately vascular. There was no inflammatory infiltration.

Fig. 2.—Photomicrograph of the adult type of striated muscle cells. Hematoxylin and eosin stain; × 300.

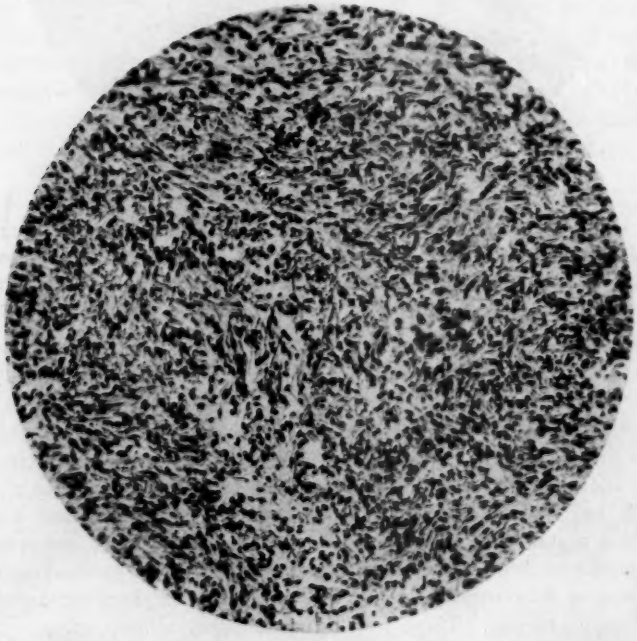

Fig. 3.—Photomicrograph of the anaplastic portion of the tumor, which resembles fibrosarcoma. Hematoxylin and eosin stain; × 110.

The anaplastic tissue was more abundant in the advancing margin of the growth. No striated fibers were seen in the subserous infiltration on the wall of the bladder or in the peritoneal extension about the ovary. The anaplastic portion was characterized by its marked cellularity. The cells showed an extreme variation in size, and all degrees of variation in shape from round to fusiform. The nuclei were not definitely hyperchromatic, though they stained darker than the nuclei of the fibroblasts in the intercellular connective tissue. Mitoses were not so frequent as was expected, considering the marked cellularity and the variation in the size and the shape of the predominating cells. The nuclear chromatin was largely distributed near the nuclear membrane. The connective tissue was abundant but not dense, and supported well formed vascular channels. The tumor cells did not line these vessels, as is frequently the case in sarcoma.

## COMMENT

Two essential problems are suggested by the tumor just described. The first may be briefly stated as follows: On what basis are we justified in saying that the tumor is not a spindle cell sarcoma? The second problem concerns the relationship between the cellular, anaplastic portion and the well differentiated portion containing the striated muscle tissue.

This tumor differs from the ordinary fibrosarcoma in the structure of the connective tissue stroma, the qualitative cellular appearances and the structure of the blood vessels. The stroma is more abundant than is normally seen in sarcomas showing an equal degree of activity in growth. The structure of the stroma is less dense and more edematous than is commonly found in a fibrosarcoma. The stroma contains fibroblasts which are not in any way to be confused with the tumor cells. The tumor cells vary in shape from round to oval and show a staining reaction different from that of the stroma cells. The cells are elongated with markedly acidophilic cytoplasm, and in many areas show cross-striation characteristic of muscle cells. The number of mitotic figures is surprisingly small in comparison with the morphologic variation in the cells. The blood vessels are well developed, and in no area do the tumor cells form the wall of a blood channel, as they so frequently do in sarcoma.

The problem of histogenesis presents greater difficulties than that of differentiation. The round cells of the anaplastic tissue appear to be typical myoblasts, and all stages in the development of differentiated striated muscle cells from the embryonic myoblasts can be found. We have not been able to trace the development of the striations from the paired centrioles through a dispersion process, as described by Wolbach.[8] However, the intimate association of the anaplastic tissue with striated muscle cells in an area where voluntary muscle is not normally found suggests that both tissues are related histogenetically. The embryologic character of this voluntary muscle tissue is further indicated by the

location of the nuclei in the center of the cell rather than beneath the sarcolemma, by the clustering of the nuclei rather than their even distribution in the length of the cell and by the presence of an abundant intercellular connective tissue.

SUMMARY

1. The extreme rarity of rhabdomyomas is noted.

2. A uterine rhabdomyoma occurring in a Negress, aged 3 years, is described clinically and pathologically.

3. The histologic differentiation of the anaplastic portion of a rhabdomyoma from a sarcoma is discussed.

# BUDDING FORMS (CONIDIA) IN CULTURES OF SPOROTRICHUM SCHENCKI

FRED D. WEIDMAN, M.D.
PHILADELPHIA

It is well known that in tissue, particularly pus, Sporotrichum schencki occurs only as budding forms; mycelia are absent. In culture, however, mycelia dominate the colony. It is true that there are reproductive bodies (conidia) which sprout abundantly from the mycelium as minute ovoid cells in smaller or larger clusters, but they are far removed morphologically and taxonomically from budding forms.

During many observations on fifteen or twenty strains of Sporotrichum in the Laboratory and in the classroom, the budding forms of conidia which I shall describe in this paper were confined to one strain and they occurred only sporadically in that strain. Meyer,[1] it is true, reported that he observed "blastomycetoid" cells in a fresh planting of pus containing Sporotrichum (from a horse) on agar, but his description was brief (only seven lines). It is conceivable that the cells had not yet become stabilized in their new saprophytic existence and retained their propensity to budding. On the other hand, it may be questioned whether the gross appearances on agar were adequate to identify the strain botanically as Sporotrichum in view of the atypical microscopic features that Meyer gave for it. His description would also hold for Monilia, since typical conidia of Sporotrichum were not mentioned. ("Long mycelia with typical clusters of spores were always absent. Macroscopically and microscopically these clusters appeared in every respect like yeast or saccharomyces.") This objection is particularly cogent in view of present-day tendencies to classify fungi on the basis of microscopic features rather than on that of the symptom complex (disease) induced or on that of the macroscopic appearance of the culture, which must have influenced Meyer in classifying his strain.

Again, Langeron [2] stated that yeast forms were observed in primary cultures from pus by Lutz and Splendore, as well as by Beurmann and Gougerot; the yeast forms did not persist in culture as they did in my own strain, being replaced by a mycelial type of growth.

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From the Laboratory of Dermatological Research, School of Medicine, University of Pennsylvania.

1. Meyer, K. F.: J. A. M. A. **65**:579 (Aug. 14) 1915.

2. Langeron, M.: Les sporotrichoses, in Roger, Widal and Teissier: Nouveau traité de médicine et de thérapeutic, Paris, Masson & Cie, 1925, vol. 4, p. 491.

Henrici,[3] too, described yeast cells in cultures of S. schencki, but they developed from germinating chlamydospores, not independently from the thallus, as is essential for the concept of conidia, whether of Sporotrichum or of any other fungus.

Budding forms were figured by Brumpt,[4] but for a different species, Rhinocladium (Sporotrichum) gougeroti. They were designated "conidies-levures." So far as they are figured in his text, they extended singly from hyphae, and not from the clusters which are much more characteristic of Sporotrichum and which were met in the strain of S. schencki with which I am concerned here.

In any event, there is evidence from several independent centers that strains of Sporotrichum are liable on rare occasion to budding formations.

It is emphasized that both the budding and the conidial forms reported here occurred in the same environment, i. e., in culture—indeed, in the same hanging drop. By way of contrast, dimorphism within a species as it grows in a differing environment, i. e., now in pus (or other tissue) and now in culture, is well known. For example, the organism of Gilchrist's disease, Blastomycoides dermatitidis, exhibits budding cells in tissue (including pus), but none in culture; in culture, mycelia and conidia are formed almost exclusively. However, here again an exception has been met in which the usual type of cell was supplemented by another; Spring [5] observed that hyphae (though abortive) were formed in the pus of an experimental mouse.

## MATERIALS, METHODS AND RESULTS

The strain studied was received from the American Type Culture Collection (no. 2,615); it had been deposited by Castellani as S. schencki in 1920. Clinical data were not available. Obviously the strain had been repeatedly subcultured. In my hands it has comported itself like S. schencki, becoming black with age; however, I have not made the agglutination and other immunologic tests that were described by Davis.[6]

Budding forms were observed on one occasion in each of four contemporaneously planted hanging drop cultures 28 days old made in Sabouraud's dextrose bouillon. On a second occasion they were observed in five or six hanging drop preparations made by students in the classroom. The general architecture of the colony, with slender hyphae and

3. Henrici, A. T.: Molds, Yeasts, and Actinomycetes, New York, John Wiley & Sons, Inc., 1930, p. 95.

4. Brumpt, E.: Précis de parasitologie, ed. 3, Paris, Masson & Cie, 1922, p. 1122.

5. Spring, D.: J. Infect. Dis. **44**:169, 1929.

6. Davis, D. J.: J. Infect. Dis. **12**:140, 1913.

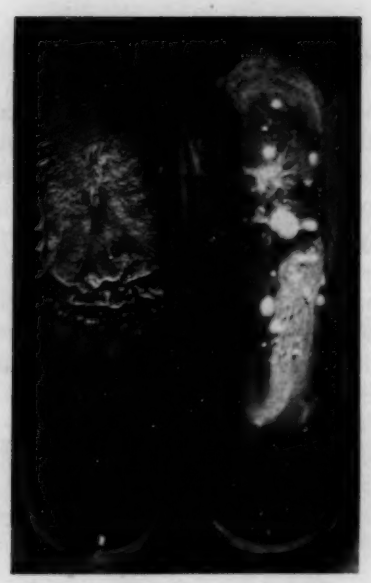

Fig. 1.—Colonies 2 months old; on Pennsylvania medium (a modified Sabouraud medium) at the left and on carrot at the right. The colonies are deep brown or black. The white portions on carrot medium indicate dissociation and compare with the "senile protuberances" described by Sabouraud.

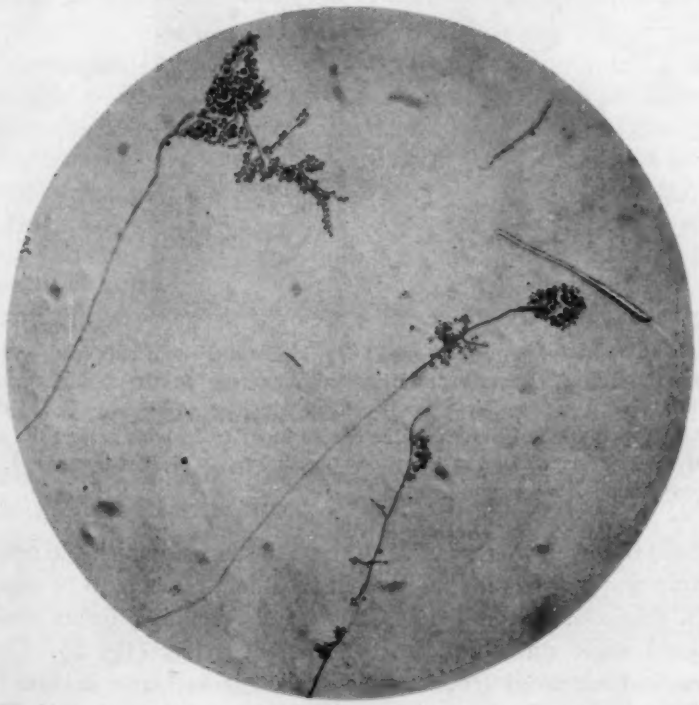

Fig. 2.—Hanging drop culture 28 days old in Sabouraud's dextrose bouillon. The more normal formations appear at the bottom of the illustration, i. e., small conidia arranged in more or less trefoil clusters at tips of lateral hyphae. The closely branched arrangement at two places higher up suggests Botrytis.

a tendency to coremium formation, was developed according to type. As usual, conidia were abundant on a comparatively slender type of mycelium, and sprang both as individuals and in clusters from its main trunks as well as from shorter or longer conidiophore hyphae. Many conidia were typically minute and apiculate, and a few extended from denticulate formations in the hyphae, such as are the basis for the genus Rhinocladium, as emphasized by Langeron.

The atypical conidia were abnormal in three respects: (1) They were swollen; (2) they were spherical, and (3) many exhibited buds. In addition, the points of attachment to the parent hyphae were most

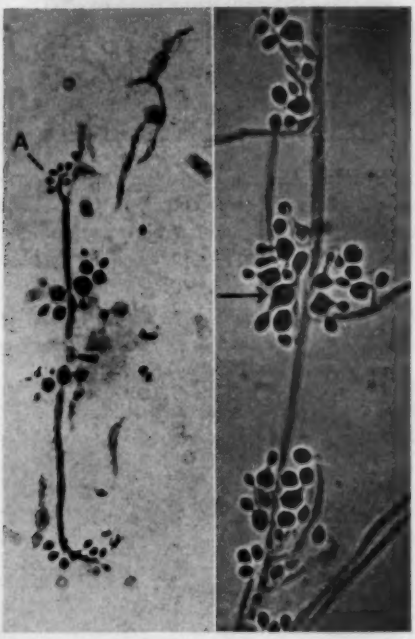


Fig. 3.—The hypha at the left shows typical Sporotrichum clustering (*A*) and the atypical budding forms, both formations occurring on the same hypha. At the right a few of the smaller, normal conidia which serve as controls are shown. Note the swollen state of some conidia (preparatory to budding?) and the occurrence of budding forms still attached to the parent hypha (marked by arrow). Two buds may extend from one cell.

indefinite; however, this was due to the late stage at which the preparation came under observation, at which time dehiscence is to be expected with S. schencki. Nevertheless, some of the budding forms could be discovered while still attached to the parent hypha (fig. 3). Usually but one bud extended from a single cell, but as many as four were sometimes discovered on special search. The question of a mixed cul-

ture did not enter since both typical conidia and budding forms could be found, although at some distance apart, *on the same hypha.* Budding forms of conidia did not occur on the dextrose-free agar of Sabouraud.

## COMMENT

*Genesis of the Budding Forms.*—The genesis of the budding forms appeared to be the same as that for conidia, i. e., growth from the lateral walls of hyphae. Indeed, the budding forms may properly be regarded as conidia which became precociously enlarged while still attached to the parent hypha, or at least promptly after dehiscence. It is axiomatic in mycology that conidia do not germinate until dehiscence, and perhaps this restraining biologic influence, while sufficient to prevent the development of germ tubes and hyphae, was not quite adequate to prevent the minor expression of germination connoted in budding.

Once well removed from the hyphae, the budding forms gave rise to germ tubes and hyphae, as shown by the presence of both buds and hyphae, which sometimes extended from the same conidium. In no case did they originate within a hyphal segment like intercalated chlamydospores. These budding forms may be looked on as temporary fugacious forms interposed in the life cycle of a protean organism such as S. schencki as the result of a vicarious abnormal urge to reproduction on the part of its conidia.

*Taxonomic Value of Budding.*—Perhaps the outstanding message from this observation, at least in the general mycologic aspect, is a reminder that the lines are not drawn hard and fast as to the production of budding forms in species of fungi. This is illustrated in various forms, for instance, between the germination of an essentially hyphal cell like a chlamydospore and that of a quasi-budding form as exemplified in certain yeastlike cells which my associates and I [7] recently observed in Acrotheca and other agents of chromoblastomycosis. Similar thoughts probably occurred to Ota [8] when he created his "pseudoblastomycosis," including sporotrichosis and chromoblastomycosis, as well as infections with Mycoderma, Scopulariopsis, and Coccidioides immitis. Indeed, the bud of the blastosporinae is but a variant of the thallospore, as illustrated by Vuillemin's classification in which the blastosporinae comprise one subdivision of the thallosporales.

In addition, this experience shows that budding may exceptionally occur as a variation under comparatively uniform conditions of culture. The medical mycologist should fully realize these limitations and grant that whereas the urge to reproduce by budding is predominant in certain species under certain conditions and is a most valuable criterion in

7. Wilson, S. J.; Hulsey, Sim, and Weidman, F. D.: Arch. Dermat. & Syph. **27**:107, 1933.

8. Ota, Masao: M. J. Aichi M. School **7**:31, 1925.

determinative work, it is not an absolute criterion. Exceptions must be expected from time to time. When met they should be accepted only at face value and with a full appreciation of the extent of the biologic vagaries rampant among fungi.

The experience in the classroom already mentioned emphasizes this. The same strain of Sporotrichum was used by over fifty students; conidia developed exclusively in the hanging drops except in five or six instances. In the latter cultures there were numerous budding forms in addition to conidia.

I do not believe that the occurrence of budding forms in this strain is sufficient to indicate a new genus, or, for that matter, a new species of Sporotrichum. Under the influence of such varying conditions as must have arisen during repeated cultures in at least three different laboratories, it is understandable that conditions such as occur in pus were sufficiently approximated from time to time to elicit the development of budding forms without at the same time preventing the development of mycelia.

The occurrence of budding cells in culture brings S. schencki closer to the "yeasts." Its moist, pasty, glistening appearance in the test tube (particularly in the early days of growth), resembling that of yeast cultures, and the budding forms observed exclusively in tissue are reconcilable with Ota's impulse to include Rhinocladium (Sporotrichum) among fungi causing the condition which he calls pseudoblastomycosis.

I disclaim any intent to overemphasize the occurrence of budding cells in cultures of S. schencki; at most it appears to be exceptional and should not influence the previously held belief as to the differing morphology of this species in pus and culture.

*Relation to Botrytis.*—In figure 2 it will be observed that in addition to the clusters of conidia which occur in the form characteristic of Sporotrichum there are large grapelike clusters. In these the conidia are borne on compact aggregations of branches which are not a usual expression of the architecture of Sporotrichum. The closeness of the branching suggests Botrytis, although it may be objected that the lateral branches do not come off perpendicularly enough and are rather lengthy. It appears that but one instance of similar formation has been recorded in the dermatologic literature, i. e., in Benedek's [9] Sporotrichum lipsiense, which was isolated from a case of dermatophytosis. Grutz criticized Benedek's determination, contending that the organism was a member of the genus Botrytis.

In any event, such a type of branching is sufficient to prompt attention to phylogenetic relationships with Botrytis, particularly since the genera Sporotrichum and Botrytis both belong to the family Botrytidae.

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9. Benedek, T.: Dermat. Wchnschr. **83**:1695, 1926.

It is further in point that the botanist has already met difficulties in this section of the taxonomic field; the imperfect stage of the ascomycetic genus Hypomyces appears variously as forms of Botrytis, Sporotrichum or Verticillium.[10]

From this, thoughts are again turned in the direction of a vegetable source in nature for Sporotrichum, as Botrytis is such an important plant parasite (being found on horse chestnut, pine and spruce trees as well as on grape vines and lettuce, bean, geranium, dahlia, primrose, strawberry and several other plants). On lemon trees it produces gummosis.[11]

SUMMARY

In a strain of S. schencki, spherical or oval budding forms occurred abundantly on the hyphae in addition to the characteristic more or less ovoid conidia. This was an exceptional phenomenon, occurring but a few times in over sixty preparations. Budding is not limited to species of fungi ordinarily classed as blastomycetes, but must be expected to emerge on occasion in other thallosporales; the occasional development of budding forms must therefore be appraised with discretion and not overemphasized taxonomically. The experience brings S. schencki closer to the "yeasts." The results recounted here should not modify the facts already established as to the characteristics of S. schencki in culture; namely, that the almost exclusive mode of reproduction is by conidia, not by budding forms. The occurrence of conidia on compact aggregations of branches may indicate affinities of Sporotrichum with Botrytis, an important parasite of a great many plants.

10. Gaumann and Dodge: Comparative Morphology of Fungi, New York, McGraw-Hill Book Company, Inc., 1928, p. 237.

11. Stevens, F. L.: Plant and Soil Fungi, New York, The Macmillan Company, 1925, p. 386.

# A SUBCUTANEOUS "MIXED" TUMOR (SALIVARY GLAND TYPE) OF THE LEFT THIGH

EDWIN F. HIRSCH, M.D.
CHICAGO

"Mixed" tumors containing mesoblastic and epithelial-like components occur commonly in the parotid gland, neck and oral regions, and in the urogenital viscera. The term "mixed" is used generally, although with some protest, to express this conglomeration of heterogeneous tissues. Islets of hyaline stroma resembling cartilage are usually present. The degree of mesoblastic tissue differentiation, the arrangement of the epithelial-like tissues and their combinations are not uniformly the same. There is, however, a close similarity in the tissue of the tumors arising in a certain region, such as in the salivary glands, the neck and the mouth.

Occasionally, mixed tumors resembling those of the salivary glands are found in some unusual part of the body. Kreibig,[1] in 1931, reported two such growths on the extremities. One of these occurred opposite the right shin of a man aged 38, at the junction of the upper and middle thirds of the leg. Six years before, he had had a "stone" bruise without external laceration; soon thereafter he noted a freely movable, pea-sized nodule that enlarged gradually and painlessly. It had grown rapidly for two years and was hard, sharply limited and readily enucleated. The periosteum and bone nearby showed no changes.

This firm tumor, the size of a hen's egg, was lobulated on the surfaces made by cutting. The tissues were mottled gray-white and translucent. Septums extended into the growth from the connective tissue capsule, dividing it into variably shaped lobules. The epithelial components were glandular structures, cell nests and cords. The glandular elements had a lining epithelium in two layers, of which the inner often was tall columnar. The lumens were empty or had eosin-stained masses and droplets. Among the solid cell cords were solitary, sharply circumscribed, circular masses of concentrically layered pavement cells, hornified in the center, and with keratin granules and intercellular bridges peripherally: a typical epithelial pearl. A few of these cell masses were edged by a single layer of regular cylindric cells; the centers were horni-

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Aided by the Winfield Peck Memorial Fund.

From the Henry Baird Favill Laboratory of St. Luke's Hospital and the Norman Bridge Pathological Laboratory of Rush Medical College of the University of Chicago.

1. Kreibig, W.: Frankfurt. Ztschr. f. Path. **42**:281, 1931.

fied. The ground substance resembled cartilage. In this interpretation, however, Kreibig made some reservations because of the variable amounts of fibrillar connective tissue or elastic fibers, the variations in cell forms and the indefinite margins of the islets. He did not consider these objections significant.

The second tumor in Kreibig's report occurred on the ventral surface of the left forearm of a man aged 30. Within three years it had grown gradually into a small hard nodule. A small defect in the superficial fascia was noted in excising the nodule, but there were no changes of the bone and periosteum. There was no recurrence three years later. Histologically, the tissue resembled closely the first tumor; both were like a mixed tumor of the parotid gland.

The only other record of such growths, according to Kreibig, was by Tessmann.[2] This nodule, larger than a cherry, was in the subcutaneous fat dorsally near the wrist between the first and second metacarpal bones of a middle-aged woman. It had developed in four years, had the structure of a mixed tumor of the parotid and had been diagnosed chondromyxo-endothelioma.

Growths described as mixed tumors have been reported also in the subcutaneous tissues of the face[3] and scalp.[4]

## REPORT OF CASE

A Negress, aged 34, was admitted to St. Luke's Hospital on Jan. 3, 1933, for the excision of a mass the size of a small apple, anterolaterally on the left thigh, the lower edge being about 10 cm. above the patella. Eight years before, she had noticed a freely movable nodule as large as a pea which gradually increased to the size mentioned. It was painless but, because of its location, frequently had been traumatized. On January 4, Dr. William B. Fisk removed the tumor with a closely adherent strip of skin. The growth lay entirely in the skin and subcutaneous tissues and did not reach beyond the deep cutaneous fascia. The surgical wound healed promptly; the patient was dismissed five days after the operation. On May 25, there was no recurrence.

The encapsulated bean-shaped mass with coarsely scalloped edges was 7.5 by 5.5 cm. and 4.5 cm. thick. A strip of dark brown, wrinkled skin tapering at each end, and 8.5 by 3.5 cm., was closely adherent on one flat side. The surfaces made in bisecting the mass were tan-brown and gray, slightly translucent tissues with a few widely distributed masses of yellow fat, and were divided into three conspicuous lobules and a small less distinct lobule (fig. 1). Thin fibrous septums separated the lobules from each other. The lobules contained masses of opaque tan-gray tissue several millimeters in diameter interspersed with more translucent tan-brown tissue. The contrast between these two tissue elements was

2. Tessmann, E.: Ueber eine Mischgeschwulst in der Gegend des Handgelenks von histologischen Character der Mischtumoren der Speicheldrüsen, Inaug. Dissert., Würzburg, 1911.

3. Brunschwig, A.: Arch. Otolaryng. **13**:52, 1931.

4. Delaney, P. A.: Arch. Path. **12**:145, 1931.

more conspicuous in some of the lobules than in others. There were a few small hemorrhages. The surfaces made by cutting were moist with a small quantity of viscid fluid.

A thin slice cut from one of the surfaces made in bisecting the mass was fixed in Zenker's solution. The tissues were embedded in paraffin, sectioned and stained with hematoxylin-eosin, phosphotungstic acid-hematoxylin, Mallory's aniline blue and van Gieson's and Weigert's elastic fiber stains. Another small piece was fixed in a trinitrophenol acid-formaldehyde solution [5] and stained according to Laidlaw's silver method.

The tissue elements were essentially of two kinds (fig. 2): masses of epithelial-like cells intermingled with stroma (islets of cartilage). The epithelial-like cells were in solid aggregates and in tubules or acini. In the solid masses they were polymorphous, about the size of cells in squamous epithelium, with an abundant acidophilic, finely granular cytoplasm and oval or round vesicular nuclei containing scattered fine and coarse chromatin granules. They were arranged compactly in

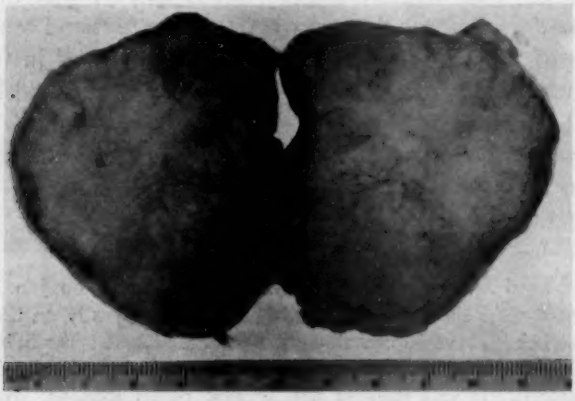

Fig. 1.—Photograph of the surfaces made in bisecting the mixed tumor of the left thigh.

mosaics, occasionally concentrically, and in a few places about round or oval masses of hyaline material not exceeding from six to eight times the long diameters of the cells. The tubular or acinar structures ranged from small ducts to the medium-sized acini of thyroid tissues. The lining cells were flattened, cuboidal or columnar epithelium, some in a single layer and others in two or possibly three layers. These tubules or acini were distinct and separate, or they were in or continuous with the compact masses of epithelial-like cells. Within their lumens were granular amorphous or colloid-like materials.

Hyaline masses resembling cartilage (fig. 3), with scalloped or roughly indented edges, formed a considerable amount of the tissues in the sections. A fibrillar, variably edematous stroma and the epithelial elements filled the interstices between them. Hyaline matrix tissues were penetrated considerably by single cells or small masses. Many large and small lacunae were in the islets of the hyaline tissue. Some of the lacunae were empty, others had a single cell or several cells

5. Solution of formaldehyde, U. S. P., 500 cc.; distilled water, 1,500 cc.; glacial acetic acid, 100 cc.; trinitrophenol to saturation point.

indistinguishable from the epithelial elements, and still others had cells angulated and like cartilage elements. Mucoid degeneration, necrosis and liquefaction were marked in some sections. In the preparation stained with phosphotungstic acid-hematoxylin, the coarse stroma in the epithelial masses had the staining qualities of collagenous fibers. The cartilage-like masses had many delicate fibers which stained sharply with Weigert's elastic tissue stain but less distinctly with the Mallory aniline blue and the van Gieson stains. In preparations stained by the Laidlaw silver method, only a few of the fibers in the masses of cartilage were blackened. The interstitial tissues had many sinuous, fine and coarse reticulum fibers. The resemblance in structure of these tumor tissues to those of a mixed tumor of the parotid gland was remarkable.

An explanation of the origin of this growth on the thigh involves theories [6] that have been proposed for mixed tumors in other parts

Fig. 2.—Photomicrograph illustrating the tissue elements in the mixed tumor of the left thigh, their arrangement, and the close resemblance to similar tumors of the salivary glands. Reduced from a magnification of × 234.

of the body. Those suggested for the histogenesis of the so-called mixed tumors of the parotid consider them as arising from (1) connective tissue endothelium, (2) epithelium alone or (3) connective tissue and epithelium. The sponsors of the first idea regard the solid strands of cells and acinar structures in the tumors as endothelial derivatives, the cartilage arising from stroma. The proponents of the epithelial origin of the tumors consider the first mentioned tissues epithelium, and the

6. Lang, J. F.: Sogenannte Mischgeschwülste der Speicheldrüsen, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 5, part 2, p. 140. Kux, E.: Virchows Arch. f. path. Anat. **280**:175, 1931. Zymbal, W. E.: Beitr. z. path. Anat. u. z. allg. Path. **91**:113, 1933.

stroma portions, in particular the cartilage-like tissues, as an epithelial product. The third and, according to Kux, the simplest explanation, is the derivation of these tumors from two germ layers, fibro-epithelial tissues; hence the origin of the mucinous and cartilaginous tissues from mesoderm.

The application of these opinions to the tumor discussed involves consideration of the tissue elements from which the growth was derived. Ricker and his students, Kreibig stated, accepted these tumors as secreting epitheliomas and assumed that epithelial derivatives of sweat glands

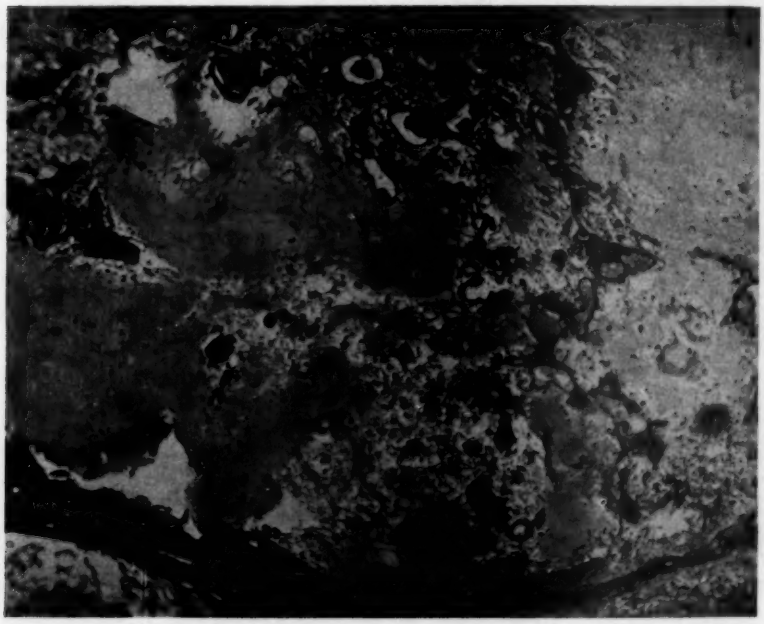

Fig. 3.—Low power photomicrograph illustrating the extensive masses of cartilage in the tumor.

may form cartilage-like and mucoid tissues. Zymbal supported the complete epithelial derivation of the mixed tumors. The theory of an embryologic displacement of tissues, proposed by Wilms [7] and others in explanation of mixed tumors, seems satisfactory for the growths that they considered. Although this may explain the few mixed tumors found on the extremities, the objections to such a conclusion are not readily dispelled. The proximity of the growth to the skin rather than to the deeper structures of the thigh, for example, is not correlated easily with mesenchymatous tissues containing cartilage.

7. Wilms, M.: Die Mischgeschwülste, Leipzig, A. Georgé, 1900.

Kistler's [8] study of the multiple islets of cartilage in a mixed tumor of the uterus suggested a growth impulse in connective tissues, stimulating focally a differentiation into cartilage. Under such conditions the stroma of an epithelial tumor arising locally in the skin or its derivatives (sebaceous or sweat glands or hair follicles) develops a hyaline matrix resembling cartilage. Kux reviewed the statements regarding the true cartilaginous character of the hyaline tissues in these tumors. He concluded that there can be no doubt regarding the presence of cartilage in these so-called mixed tumors, but his studies did not establish whether the cartilage was heterologous, accessory or secondary, or primary. The dense network of elastic fibers in the ground substance, he stated, indicated a secondary origin because elastic fibers are typical of such accessory cartilage formations. Such a view agrees with Kistler's: the development of cartilage in fibrous stroma.

SUMMARY

A clinically benign mixed tumor grew slowly for nine years in the subcutaneous thigh tissues of a Negress. The structure of this growth resembled mixed tumors of the parotid gland.

8. Kistler, G. H.: Am. J. Cancer **16**:399, 1932.

# NEUROMATOSIS OF THE VERMIFORM APPENDIX

KIYOSHI HOSOI, M.D.
NEW ORLEANS

In 1921, Masson [1] and Maresch [2] reported the finding of neuromatous tumors in obliterated appendixes. At that time they believed that these growths were of the nature of amputation neuromas, because they thought that they were caused by a division of the sympathetic filaments of the mucosa by an ulcerative process or by injury to the nerves by an inflammatory process. In 1922 Schweizer [3] found neuromatous structures in 40 per cent of 12 obliterated appendixes removed for chronic appendicitis and in 60 per cent of 20 obliterated appendixes obtained post mortem. He concluded that these were neurinomas of Verocay. Neurogenic appendicitis (neuromatosis) was observed 16 times by Urech [4] in the course of the last 400 appendectomies performed in the Surgical Clinic of Lausanne. Of the 16 appendixes, 4 were removed because of acute pain; 3 of these showed no gross or microscopic evidence of inflammation, and in 1, phlegmonous appendicitis was engrafted on the neurogenic appendicitis. This case of Urech's reminds one that secondary inflammation in a neuromatous appendix is a possibility that must be thought of in the clinical diagnosis of neurogenic appendicitis. In the routine examination of a retrocecal obliterated appendix obtained at necropsy from a 70 year old woman, Barth,[5] in 1929, observed an axial neuroma and a simultaneous proliferation of carcinoid tumor cells. Masson [6] has recently stressed the close interrelationship between neuroma and chromo-argentaffin or carcinoid cells; he showed that the latter are always present in the growing or fully developed axial neuroma of the obliterated appendix, and that the neuromas regress and are absorbed if the argentaffin cells disappear. These

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From the Department of Surgery, Tulane University School of Medicine, New Orleans, and the Department of Pathology, Albany Medical College, Albany, N. Y.

1. Masson, P.: Lyon chir. **18**:281, 1921; Compt. rend. Acad. d. sc. **173**:262, 1921; Congrès de médecine, Strasbourg, 1921. Compt. rend. de l'Assoc. d. anat., 1922, p. 217; Neural Proliferations in the Vermiform Appendix, in Penfield, Wilder: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, sect. 25, p. 1095.
2. Maresch, R.: Wien. klin. Wchnschr. **34**:181, 1931.
3. Schweizer, P.: Schweiz. med. Wchnschr. **52**:1202, 1922.
4. Urech, E.: Rev. méd. de la Suisse Rom. **48**:425, 1928.
5. Barth, H.: Virchows Arch. f. path. Anat. **273**:62, 1929.
6. Masson, P.: Am. J. Path. **4**:181, 1928.

intranervous argentaffin cells spring by a process of budding from the epithelium of the glands of Lieberkühn and migrate out into the periglandular plexus. Masson showed that appendicular neuromas arise from the nerves of the periglandular plexus, and that they regress individually. Picard and Appelmans'[7] patient, a man, aged 26, complained of persistent pain in the right iliac fossa over McBurney's point but showed no muscular rigidity. Three months previously, he had a typical attack of acute appendicitis with fever. Operation revealed a neuroma, from 3 to 3.5 cm. in diameter, in the proximal half of an obliterating appendix.

In addition to the argentaffin cell neuroma just described, sympathetic neuroma and neurofibroma can occur in the appendix. The presence of ganglion cells in sympathetic neuroma (ganglioneuroma) has been reported by Oberndorfer[8] and by Schultz.[9] These cells were accidentally found in the routine examination of postmortem material in Schultz' case (a man, aged 57). However, Oberndorfer's patient, a man 28 years old, was operated on for acute perforated appendicitis, and the operation revealed a primary giant growth of the appendix combined with ganglioneuromatosis of the same organ. The appendix was more than 16 cm. long. Associated with the rich number of nerve fibers, there were extraordinary huge masses of ganglion cells which were in part arranged in groups so that they could be seen macroscopically in the stained sections. The mesentery of the appendix showed typical neurofibromatosis; the body, too, was covered with tumors and showed extensive pigmentation of the skin, all typical of Recklinghausen's disease (multiple neurofibromatosis). Pick[10] believed that Oberndorfer's case was not associated with ganglioneuromatosis but with neurinomatosis. This brings up the old dispute whether these multiple tumors of nerve trunks are neurofibromatous (hence mesodermal in origin) or neurinomatous and schwannian (hence ectodermal in origin). The discussion of this dispute is only of theoretical interest and need not be taken up here. In Peritz'[11] patient, a woman of 73 years, who had a sudden onset of vomiting and pain in the right lower quadrant, but no increase in temperature or in the leukocyte count, operation showed a neurinomatous tumor mass of the appendix. Schmincke[12] described a neurinomatous formation both in the obliterating appendix and in the meso-appendix. Hoey's[13] patient, a man,

7. Picard, E., and Appelmans, R.: Rev. belge sc. méd. **1**:241, 1929.
8. Oberndorfer: Ztschr. f. d. ges. Neurol. u. Psychiat. **70-72**:105, 1921.
9. Schultz, A.: Centralbl. f. allg. Path. u. path. Anat. **33**:172, 1923.
10. Pick, L.: Beitr. z. path. Anat. u. z. allg. Path. **71**:560, 1922-1923.
11. Peritz, L.: Zentralbl. f. Chir. **57**:2475, 1930.
12. Schmincke: Centralbl. f. allg. Path. u. path. Anat. **33**:17, 1922.
13. Hoey, T.: Brit. M. J. **2**:490, 1928.

aged 47, who had Recklinghausen's disease, complained of intermittent colicky pains in the abdomen, later localizing in the right lower quadrant, where he had since felt a tender swelling. The temperature was 97 F.; the pulse rate, 72, and the respiratory rate, 20. The pathologic report was neurofibroma of the appendix.

Probably one of the first to describe this peculiar giant anomaly of the intestinal tract was Lotz,[14] who studied a specimen of horse intestine, 55 cm. long, about two thirds of which was markedly thickened and of giant size so that the wall was 22 mm. thick. Meissner's plexus was truly of gigantic dimensions, containing numerous ganglion cells. The mesentery, strictly corresponding to the giant growth, showed plexiform tumor masses of the splanchnic nerve. Pick [10] cleverly described this giant growth as if the intestines of a much larger giant animal had been anastomosed into the intestines of the horse. Cases of markedly enlarged appendixes reported in the American literature by Howard [15] (12.5 by 8.8 cm.), Strong [16] (15 by 6.3 cm.), Williams [17] (10 by 3.5 cm.) and others in all probability belong to this group of giant growth and indicate that secondary inflammation may help to swell the already large appendix and give rise to acute symptoms. Lotz, Pick and Holz [18] concluded that they could see no etiologic relationship between neurofibromatosis of the mesenteric nerves and the giant growth of the intestinal segment; they believed that both were coordinated congenital malformations.

Can it be that this association of giant growth of the appendix or of an intestinal segment and neurofibromatosis or their corresponding mesenteric nerves is only fortuitous? Pick and Bielschowsky [19] and Winestine [20] reported the same case of a man, aged 60, who presented symptoms of sharp abdominal pain over variable periods, diarrhea, rectal incontinence, tenesmus and periods of obstipation. Necropsy revealed multiple neurofibromatosis of the lumbar and pelvic sympathetic nerves and adenomatous polyposis of the rectum. The topographically intimate and exact relationship between this adenomatous blastomatosis of the rectal mucosa and the neurofibromatosis of that

14. Lotz, A. C. L.: Der partielle Riesenwuchs mit besonderer Berücksichtigung des sogenannten sekundären, eine pathologisch-anatomische Untersuchung, Inaug. Dissert., Berlin, G. Schade, 1914.

15. Howard, W. F.: Northwest Med. **4**:110, 1912.

16. Strong, S. M.: Am. J. Surg. **28**:472, 1914.

17. Williams, C.: Virginia M. Monthly **52**:569, 1925.

18. Holz, H.: Ueber fortschreitenden partiellen Riesenwuchs, Inaug. Dissert., Frankfurt, 1919.

19. Pick, L., and Bielschowsky, M.: Centralbl. f. allg. Path. u. path. Anat. **33**:172, 1922-1923.

20. Winestine, F.: J. Cancer Research **8**:409, 1924.

particular segment of the rectal nerves was striking. Winestine concluded that there is a syntropic combination of neurofibromatosis with pure blastomatosis, paralleling the combination of neurofibromatosis and true giant growth. In a review of the literature of multiple neurofibromatosis, I [21] found that Recklinghausen's disease is often associated with one or more types of tumors, this very multiplicity of different tumors connoting an underlying congenital defect, probably due to dysontogenetic influences.

## EXAMINATION OF 195 CASES OF NEUROMATOSIS OF THE VERMIFORM APPENDIX

For this study, the 344 consecutive vermiform appendixes removed at operation and showing no evidences of acute inflammation were fixed in a diluted solution of neutral formaldehyde, U. S. P. (1:10), Zenker's fluid and a formaldehyde-trinitrophenol solution.[22] Many microscopic sections, serial and otherwise, were cut from three or four different portions of the appendix and stained with hematoxylin and eosin, van Gieson's trinitrophenol-fuchsin, Mallory's phosphotungstic acid-hematoxylin,[23] Laidlaw's lithium silver,[24] Foot and Mènard's ammonium silver [25] and Masson's trichrome.[6] A detailed study of these 344 appendixes revealed neuromatosis in 195.

*Description of Neuroma.*—The gross appearance of appendixes the seat of neuromatous growths is mostly normal, there being nothing characteristic to indicate the presence of such tumors. In a few cases, the distal portion of the obliterated appendix was slightly enlarged in a fusiform or bulbous manner, but other benign tumors such as carcinoids, fibroma and myoma present similar enlargements. The lumen of the majority of appendixes was partially or completely obliterated. Most of these neuromatous growths were of microscopic size. When they were large enough to be noticeable grossly, the cut surface appeared opaquely grayish-white.

For the study of microscopic sections in the identification of neuroma, the Masson trichrome stain was found to be the best. Very often minute groups of neuromatous tissue will escape detection when other staining methods are used. If the sections are properly stained, the Masson method quickly picks out and identifies the neuromas as red

21. Hosoi, K.: Arch. Surg. **22**:258, 1931.

22. Formaldehyde-trinitrophenol solution is made up as follows: solution of formaldehyde, U. S. P., 500 cc.; distilled water, 1,500 cc.; glacial acetic acid, 100 cc.; trinitrophenol to saturation point.

23. Mallory, F. B., and Wright, J. H.: Pathologic Technique, ed. 8, Philadelphia, W. B. Saunders Company, 1924.

24. Laidlaw, G. F.: Arch. Path. **8**:363, 1929; Am. J. Path. **5**:239, 1929.

25. Foot, N. C., and Mènard, M. C.: Arch. Path. **4**:211, 1927.

loosely anastomosing strands of nonmedullated nerve fibers (fig. 1) or as red islands of compact interlacing bundles in a field of deep blue, the blue representing the tinctorial reaction of the fibrofatty tissue composing the axial core of the obliterated appendix. Whenever the muscularis mucosae is intact, the neuromas are seen to lie central to it (fig. 2). Indeed, the neuroma if large enough may fill the entire

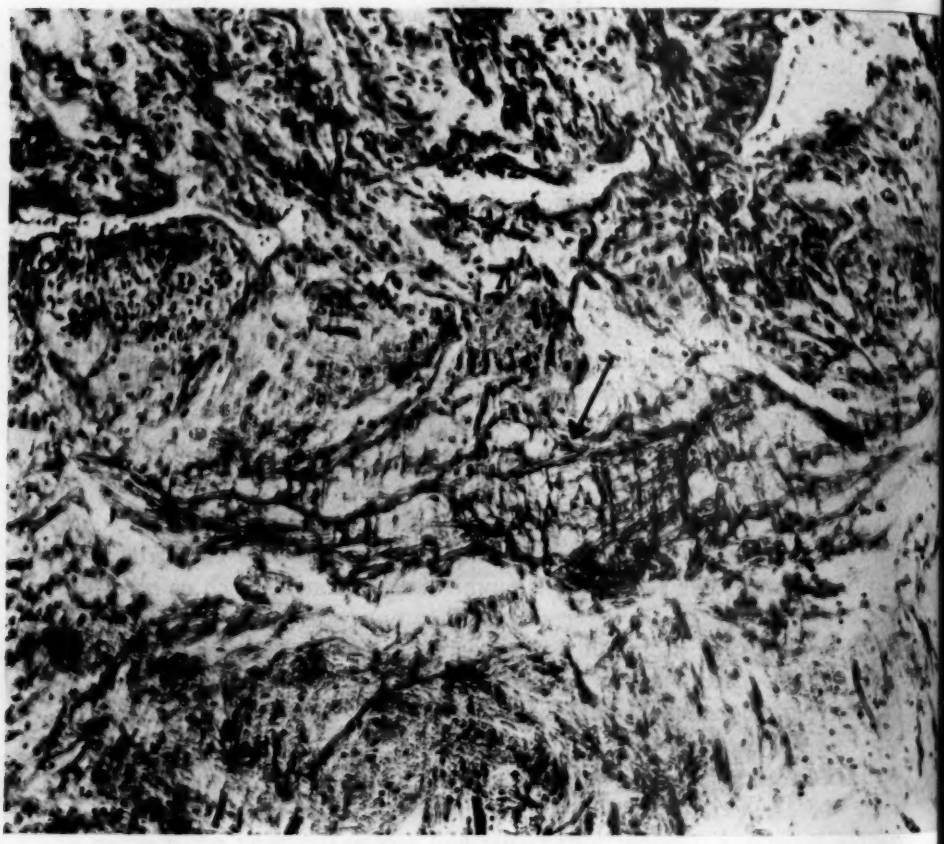


Fig. 1.—Photomicrograph of the axial portion of a completely obliterated appendix, showing the loosely anastomosing, large, nonmedullated nerve fibers (arrow). Masson's trichrome stain; × 213.

central space with the muscularis mucosae closely apposed to it along the periphery in the manner of a capsule (fig. 3). The neuroma rarely breaks through this muscularis mucosae and extends into the submucosa. The number of neuromas may vary from one to many. When multiple, they are linked together by many nerve fiber strands, which stretch across from tumor to tumor like telephone wires. These neuromas contain a variable admixture of either argentaffin cells or lymphocytes.

Masson considers these neuromas infiltrated with lymphocytes to be undergoing retrogression. In the nonobliterated, still patent appendix, these neuromas can be easily found in the mucosa by the use of Mallory's phosphotungstic acid-hematoxylin stain and positively identified by Masson's trichrome stain. When treated with silver stains, it is observed

Fig. 2.—Photomicrograph of the axial portion of a completely obliterated appendix to show the still persistent muscularis mucosae (arrows) surrounding a few neuromas. Note the strands of nerve fibers running from one tumor nodule to another. Masson's trichrome stain; × 133.

that the nonmedullated fibers are supported by a lacy network of very fine reticulum, having an intricate honeycombed appearance (fig. 4).

*Incidence.*—Among the 344 appendixes examined microscopically, there were 195, or 56.7 per cent, in which axial neuromas were found. Other rare and interesting findings were minute calcified bodies in the serosa and tuberculosis of the mucosa in 1 case each. One hundred

and sixty-five, or 48 per cent of all the appendixes, had a partially or completely obliterated lumen. Of the 195 cases of neuroma, 135, or 69.2 per cent, occurred in obliterated appendixes, and 60, or 30.8 per cent, in nonobliterated ones. The incidence of neuroma for all obliterated appendixes would then be 82 per cent, which figure closely agrees with Masson's 86 per cent.

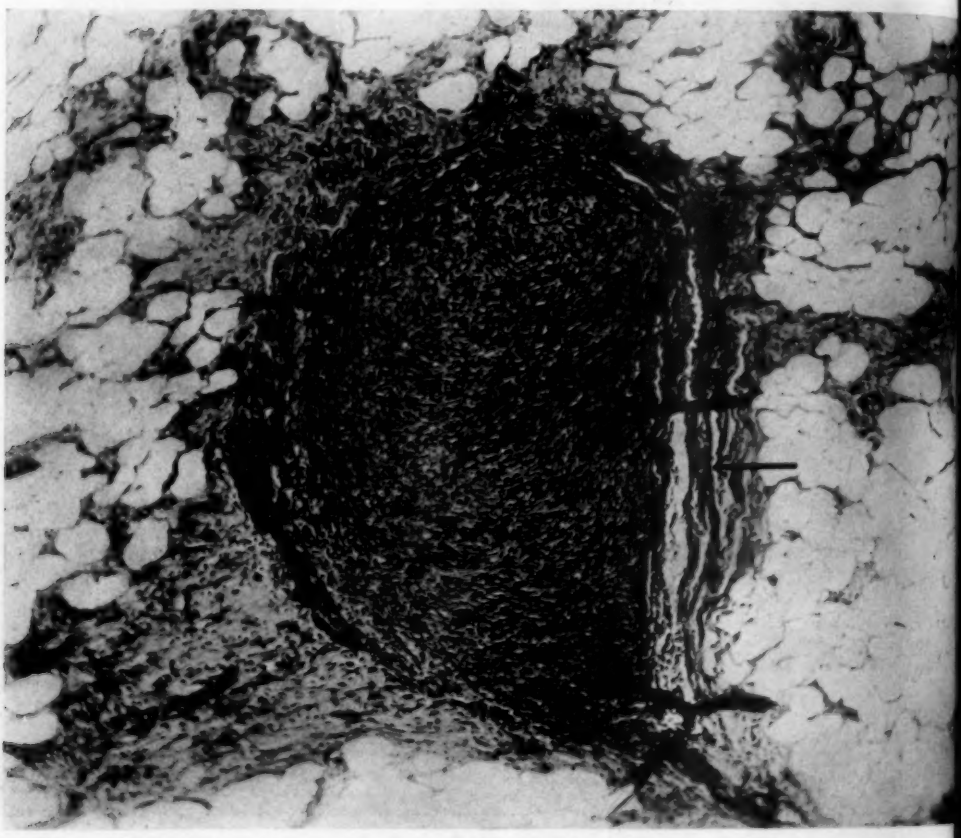


Fig. 3.—Photomicrograph of a well developed neuroma completely surrounded by the still persistent muscularis mucosae, simulating a capsule (arrow). Note the compact interlacing strands of nerve fibers. Masson's trichrome stain, × 133.

The following short summaries of 6 representative cases are appended to show that neuromatosis of the appendix may simulate acute appendicitis, acute exacerbation of chronic appendicitis or chronic appendicitis. In neuromatosis, in spite of the apparent acuteness of the symptoms, the temperature and white blood count tend to remain within normal limits. Physical examination may even reveal a rigid abdomen, especially in the right lower quadrant, plus marked tenderness. In some cases, a rebound tenderness was present, and a test of the psoas

muscle was positive. The patient's agony may be so extreme that he literally doubles up or rolls about, trying to obtain relief; or his complaint may be merely of a dull ache or discomfort in the right lower quadrant with only a slight tenderness at McBurney's point. Nausea, with or without vomiting, ranged from mild to severe, and the attacks varied in number from one to many.

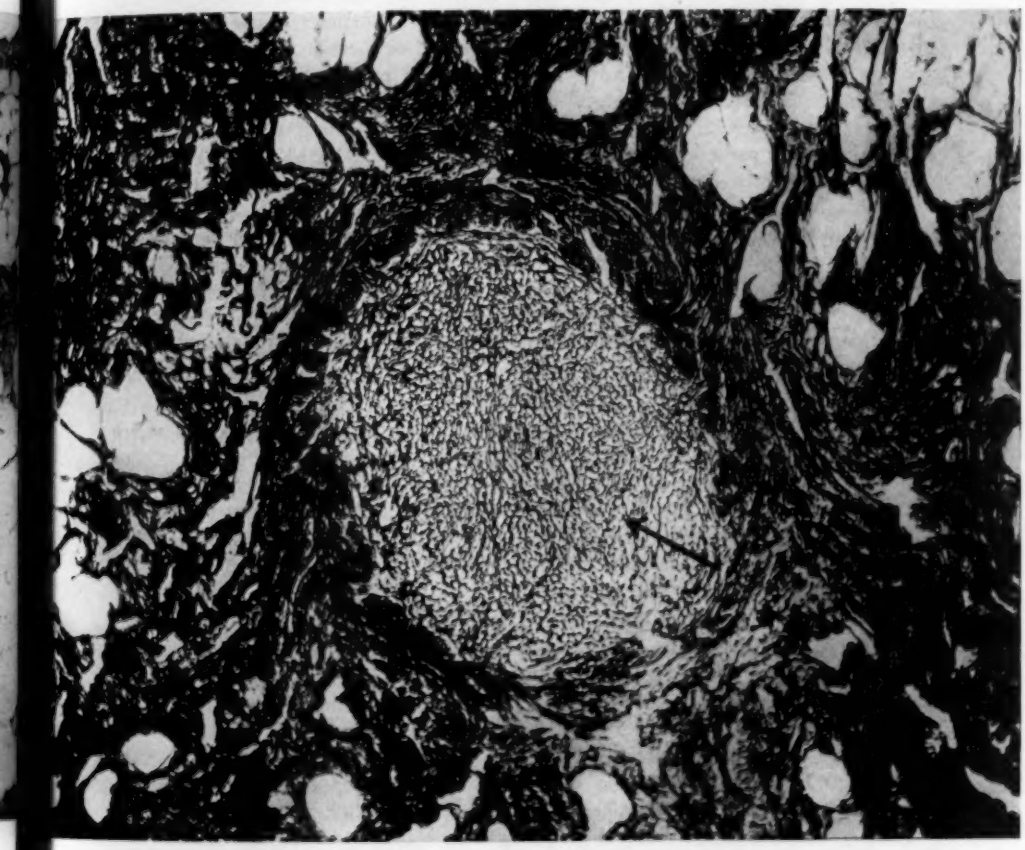


Fig. 4.—Photomicrograph of a neuroma to show the intricate lacy network of reticulum (arrow) forming a supportive tissue for the nerve fibers. Laidlaw's silver stain; × 134.

## REPORT OF REPRESENTATIVE CASES OF APPENDICULAR NEUROMATOSIS

CASE 1.—A man, aged 28, the day previous to admission was taken with severe pain around the umbilicus which radiated to the right lower quadrant. He described it as a feeling as though something was pulling on his navel from the inside. He was extremely nauseated and had to lie down. There were considerable pain and distress all night. On the morning of admission, the pain was localized in the right lower quadrant.

When the patient was 19 years old, he had a similar attack, which subsided in a few days under treatment by a physician. Over six months prior to admission, he had another colicky attack.

Physical examination showed marked tenderness in the right lower quadrant, both on pressure and on the rebound. Some tenderness was also elicited in the right flank. There was definite muscular spasm in the right lower quadrant. No palpable mass was felt in the abdomen. Rectal examination revealed tenderness on the right side. Urinalysis gave negative results. The white blood count was 5,900; a differential count gave 68 per cent polymorphonuclear leukocytes and 32 per cent lymphocytes. The temperature, pulse and respiration were normal. The patient was operated on for acute appendicitis, but only an obliterated appendix was found. No other pathologic process was found in the abdominal cavity.

Case 2.—A woman, aged 31, prior to admission was seized with a dull cramping pain in the right lower part of the abdomen, which lasted about three days. She was nauseated but did not vomit. After that she had two similar attacks. Four days before admission, the fourth and most severe attack occurred, with much nausea but no vomiting. She had to stay in bed. Physical examination showed definite tenderness over McBurney's point and moderate spasm of the right rectus muscle. There was tenderness in the right vault on bimanual examination. The temperature, pulse and respiration were normal. Urinalysis gave negative results. The appendix removed at operation was of the obliterated variety; there was no pathologic condition of the pelvis. Figure 4 shows the microscopic changes.

Case 3.—A woman, aged 37, following an attack of grip, experienced severe abdominal pains. At first, the pain was low in the right lower quadrant just above the inguinal ligament; later, it was slightly higher. She was in bed for seven weeks and had experienced some pain ever since. Examination showed tenderness in both lower quadrants, most marked on the right, with a good deal of rigidity of the right lower quadrant. Urinalysis gave negative results. The temperature was 98 F.; the pulse rate, 95, and the respiratory rate, 20. The appendix was found to be completely obliterated, without adhesions.

Case 4.—A woman, aged 27, five days before admission began to have pain in the right lower quadrant, which was dull and constant, never sharp and severe. She did not sleep well that evening. The dull pain continued for the next two days. There was no nausea, vomiting, diarrhea, dysuria, chills or fever. The pain disappeared the day before admission and had not recurred. In the past, there was occasional indigestion with pains in the lower part of the abdomen, not at all severe. On physical examination, only a slight tenderness in the right lower quadrant was present. Urinalysis gave negative results. The temperature, pulse and respiration were normal. The appendix was found to be completely obliterated but nonadherent.

Case 5.—A girl, aged 18, for the past three weeks had considerable pain in the right side. The pain started in the right side, and lasted for a day or so. It then went to the epigastric region and later returned to the right side. There had been no vomiting until two days prior to admission, when the patient became nauseated and vomited. Her bowels had been regular. During the last day or so, the pain had been worse. Examination showed tenderness and spasm over McBurney's point. The temperature was normal. Urinalysis gave negative results. At operation, the appendix was nonadherent and its lumen patent.

Case 6.—A woman, aged 25, entered the hospital with the chief complaint of severe cramplike abdominal pain, more pronounced in the right lower quadrant. The pain came on suddenly and became progressively worse until admission. She

vomited only once. For the past three days she had a general digestive upset and became constipated. She had a similar attack two months prior to admission. On physical examination, there was great tenderness in the lower part of the abdomen, more marked in the right iliac region. The temperature was 98 F.; the pulse rate, 100, and the respiratory rate, 23. Urinalysis gave negative results. At operation, the appendix was grossly normal in size and shape, but was completely obliterated and bound down by adhesions. The gallbladder, stomach, fallopian tubes and ovaries were normal.

## SUMMARY

Of 344 vermiform appendixes removed consecutively at operation and showing no evidence of acute inflammation, 165, or 48 per cent, had a distally or totally obliterated lumen and 195, or 56.7 per cent, showed neuromatosis.

Of the 195 cases of neuromatous growths, 135, or 69.2 per cent, occurred in obliterated appendixes and 60 cases, or 30.8 per cent, in nonobliterated ones. This gave an incidence of 82 per cent of neuromatous appendixes for all obliterated appendixes.

There was nothing characteristic grossly to indicate the presence of appendical neuromatoses. When the neuromatous growth was grossly noticeable, its cut surface appeared opaquely grayish white, usually without well demarcated borders. The larger growths in this series measured not more than from 1.5 to 2 mm. in diameter.

The number of neuromatous growths varied from one to many. When multiple, they were linked together by many nerve fiber strands. They appeared as loosely anastomosing strands of nonmedullated nerve fibers or as islands of compact interlacing bundles of spindle-shaped cells, always located central to the muscularis mucosae. If the neuromatous tumor mass was large enough, the muscularis mucosae was closely apposed to it along the periphery in the manner of a capsule. Rarely the tumor mass broke through the muscularis mucosae. These neuromatous growths contained a variable admixture of either argentaffin cells or lymphocytes.

The Masson trichrome stain should be employed before an appendix is discarded as being negative for neuromatosis.

# LYMPHOCYTES IN THE PERIPHERAL BLOOD OF RABBITS FOLLOWING INJECTION OF FOREIGN SUBSTANCES

I. T. ZECKWER, M.D.

K. C. BARTLETT, A.B.

G. A. SCHWARZ, A.B.

AND

R. M. SHAPIRO, B.S.

PHILADELPHIA

The experiments reported in this paper are continuations of experiments previously reported by one of us,[1] in which the leukopenia and following leukocytosis induced by injections of sodium nucleinate and of vaccine were studied chiefly with regard to the total white cell count and the granulocytes. In the course of these experiments certain casual observations were made on the disappearance from the peripheral blood stream of the nongranular white cells and on their rate of reappearance. The data of these former experiments have been analyzed anew from the point of view of gaining information on the nongranular cells rather than on the granulocytes, and a number of new experiments have been carried out solely with this point in mind.

Ever since Arneth's [2] study of the effect of intravenous injections of various substances that cause a shift of the granulocytes to the left, an overwhelming amount of evidence has established some of the fundamental facts about the response of the granulocytes to foreign substances. To any one accustomed to injecting foreign substances intravenously into rabbits it is a commonplace observation that almost any kind of substance, especially proteins but also certain nonproteins, will cause an immediate peripheral leukopenia owing to redistribution of the white cells between the periphery and the deep viscera, which is followed in a few hours by a leukocytosis in which young forms of granulocytes are obviously numerous and which, therefore, represents increased delivery of new cells from the bone marrow.

In comparison to what is known about the granulocytes, little is known about the lymphocytes in regard to such matters as the possible

From the Department of Pathology, University of Pennsylvania Medical School.

1. Zeckwer, I. T.: Arch. Path. **7**:1012, 1929.

2. Arneth, J.: Die qualitative Blutlehre, Leipzig, Dr. Werner Klinkhardt, 1920.

redistribution of cells within the vascular system, the conditions under which temporary peripheral lymphopenia may occur, the rate of the return of the lymphocytes to the previous level after temporary disappearance from the periphery, and the rate at which an absolute increase in the number of lymphocytes of the blood may be induced. Furthermore, attempts to recognize young forms of lymphocytes and to establish a "shift to the left" for the lymphocytes merit further study. The experiments reported in this paper were carried out in an attempt to elucidate some of these points.

## EXPERIMENTAL PROCEDURE

Rabbits were used. For the leukocyte counts they were bled from a small incision in the marginal vein of the ear, care being taken to secure freely flowing blood. Every attempt was made to keep the animals free from excitement and vasomotor changes and to maintain their normal posture. A number of counts and smears were made before the foreign substances (suspensions of killed Bacillus coli or sodium nucleinate) were injected. Twenty-four hour cultures of B. coli on agar, suspended in salt solution, were killed, some in a water bath at 60 C. and others by autoclave. Sodium nucleinate was used in many experiments because, being nonprotein, it could be injected repeatedly without our having to consider the development of sensitization or immunization and because it was even more effective than foreign proteins in producing the phenomenon to be studied. Most of the sodium nucleinate used was dissolved in distilled water and brought just to the boiling point in order to sterilize it. One batch was autoclaved and therefore may represent disintegration products of sodium nucleinate. In a few experiments nucleic acid was dissolved in weak sodium hydroxide. The agent used is indicated in the table.

Blood films were stained by Wright's method or by superimposing Giemsa's stain on an unwashed Wright stain (Wiseman [3]). Following the intravenous injections, films and total white cell counts were made at varying intervals and the percentage values of cells translated into absolute values. In the films stained by the special stain, the lymphocytes were classified as to age on the basis of the degree of basophilia, according to the criteria of Wiseman. In the table, lymphocytes and monocytes are grouped together as nongranular cells.

In nine rabbits, splenectomy was carried out under aseptic conditions. A number of days later, the cellular response to the injections was studied.

## RESULTS

Experiments 1 to 8 were the experiments in which the data on granulocyte counts were published but in which the data on lymphocytes were not described.[1] Experiments 9 to 18, the data on which have not previously been published, were experiments carried out with the sole purpose of studying the nongranular cells.

*Involvement of Nongranular Cells as Well as of Granulocytes in the Peripheral Leukopenia Following Injections.*—In every experiment,

3. Wiseman, B. K.: J. Exper. Med. **54**:271, 1931.

*Data on Eighteen Experiments*

| Experiment | Rabbit | Date | Experimental Condition | Injection | Gm. Injected | Time in Hours When Nongranular Cells Rose from Lymphopenic Level | Time in Hours When Granulocytes Rose from Leukopenic Level |
|---|---|---|---|---|---|---|---|
| | | | I. Effects of Injection of Suspensions of B. Coli | | | | |
| 1 | 1 | 9/13/28 | Animal intact | 1st* | .... | Not within 4½ | Before 4½ |
| | | 9/19/28 | 5 days after splenectomy; white blood cells, 16,000 | 2d* | .... | Not within 6 | Before 3 |
| | | 9/26/28 | 12 days after splenectomy; white blood cells, 22,800 (infected leg) | 3d* | .... | Not within 6 | Before 3½ |
| 2 | 3 | 9/17/28 | Animal intact | 1st* | .... | Not within 6½ | Before 4½ |
| | | 9/24/28 | 4 days after splenectomy | 2d | .... | Not within 3 | Before 2 |
| 3 | 5 | 10/16/28 | 11 days after splenectomy | 1st | .... | Before 20 | Before 20 |
| | | 10/19/28 | 14 days after splenectomy | 2d | .... | Not within 3 | Before 3½ |
| | | | II. Effects of Injection of Sodium Nucleinate | | | | |
| 4 | 8 | 10/29/28 | Animal intact | 1st | 0.15 | Before 24 | Before 24 |
| | | 10/31/28 | Animal intact | 2d | 0.10 | Before 24 | Before 24 |
| | | 11/ 1/28 | Animal intact | 3d | 0.05 | Before 24 | Before 24 |
| | | 11/ 8/28 | Animal intact | 6th | 0.10 | Before 23 | Before 23 |
| 5 | 10 | 11/20/28 | 14 days after splenectomy; white blood cells, 27,000 (infected leg) | 2d | 0.10 | Before 3 | Before 2½ |
| 6 | 11 | 11/27/28 | Animal intact | 1st | 0.50 | Before 7 | Before 7 |
| | | 12/ 5/28 | Animal intact | 2d | 0.50 | Before 5½ | Before 5½ |
| | | 12/11/28 | 5 days after splenectomy | 3d | 0.50 | Before 3½ | Before 3½ |
| 7 | 12 | 11/26/28 | Animal intact | 1st | 0.10 | Not within 5½ | Before 5½ |
| | | 12/ 3/28 | Animal intact | 2d | 0.10 | Not within 6 | Before 5 |
| 8 | 13 | 12/ 4/28 | Animal intact | 1st | 0.10 | Between 3½ and 4 | Between 3½ and 4 |
| | | 12/12/28 | Animal intact | 2d | 0.10 | Before 7 | Before 7 |
| 9 | 93 | 2/26/32 | Animal intact | 1st | 0.20 | Before 20 | Before 20 |
| 10 | A | 4/ 3/32 | Animal intact | 1st | 0.20* | Not within 4 | Before 3 |
| | | 4/12/32 | Animal intact | 2d | 0.20* | At 4 | At 4 |
| | | 6/17/32 | Animal intact | 3d | 0.20 | Before 12 | Before 12 |
| 11 | B | 4/17/32 | Animal intact | 2d | 0.20* | Not within 3 | Before 2 |
| | | | | 3d | 0.20* | Before 15 | Before 15 |
| | | | | 4th | 0.20* | Before 25 | Before 25 |
| 12 | C | 4/ 7/32 | Animal intact | 1st | 0.20* | Not within 5 | Before 4 |
| | | 4/13/32 | Animal intact | 2d | 0.20 | Before 15 | Before 15 |
| | | 6/16/32 | 10 days after splenectomy | 2d | 0.20 | Before 16 | Before 15 |
| 13 | D | 4/14/32 | Animal intact | 1st | 0.20 | Before 21 | Before 21 |
| | | 6/23/32 | 17 days after splenectomy | 2d | 0.20 | Before 20 | Before 20 |
| 14 | E | 4/11/32 | Animal intact | 1st | 0.20 | At 8 | At 4 |
| | | 6/23/32 | 28 days after splenectomy | 2d | 0.20 | At 7 | At 4 |
| 15 | F | 4/12/32 | Animal intact | 1st | 0.20* | Before 3 | Before 3 |
| | | 6/17/32 | Animal intact | 2d | 0.20 | Before 17 | Before 17 |
| 16 | 94 | 6/16/32 | Animal intact | 1st | 0.60* | Before 25 | Before 25 |
| 17 | G | 6/ 8/32 | 1 month after splenectomy | 1st | 0.20 | Before 5½ | Before 4 |
| 18 | 100 | 1/13/33 | Animal intact | 1st | 0.20 | At 9 | At 4 |

* Autoclaved.

the absolute number of nongranular cells dropped as rapidly as that of the granulocytes (chart).

Although we did not make lymphocyte counts on blood from the viscera, it is reasonable to assume that the rapid disappearance of these cells from the peripheral circulation means accumulation in the deep viscera. The simultaneous disappearance of nongranular cells and


Response of intact rabbit 100 (experiment 18) to the first injection of sodium nucleinate; *M* signifies lymphocytes of medium age; *Y*, young lymphocytes.

granulocytes from the periphery lends support to the theory that vasomotor changes may be a factor in the redistribution of leukocytes, a point that will be discussed later.

*Time of Increase of Nongranular Cells in the Peripheral Circulation in Relation to That of Granulocytes.*—It will be seen from the table that the return increase of nongranular cells after the leukopenic period was in a few experiments almost coincident with the increase of the

granulocytes (experiments 6, 8, 10, 15 and 17), but that in most experiments the nongranular cells lagged behind the granulocytes, as is shown in the chart. When the granulocyte count was high, owing to infection or a previous injection, the granulocytes responded especially rapidly (experiments 1 and 5). Consideration was given to the well established fact that the number of leukocytes fluctuates enormously from time to time under physiologic conditions. Therefore fluctuations were not considered significant unless the levels reached differed greatly from the preinjection ones, and were well beyond the limits for normal given by Pearce and Casey [4] and others for the rabbit.

Whitney [5] recently reviewed some of the literature on lymphocytosis. Doan and his co-workers [6] "never observed a subsequent lymphocytosis of any moment" after injections of sodium nucleinate, and recently Doan [7] reported that after often-repeated injections of nucleinate a relative and absolute lymphopenia occurs. Among recent studies on the production of lymphocytosis, Wiseman gave data on lymphocytes in rabbits with active tuberculous infection [8] and after repeated injections of protein,[8] and Ehrich [9] gave data on lymphocytes after subcutaneous infection of rabbits with staphylococci and after repeated intravenous injections of killed staphylococci. Most of the work mentioned dealt with repeated injections or with infections in which the organism was continuously alive. In our experiments we were dealing with the effect of a single injection and with the effect of several subsequent injections. In 5 rabbits we found a slight increase in lymphocytes, roughly up to double the original values, about twenty-four hours after injection.

*Types of Lymphocytes in the Peripheral Blood Under the Given Experimental Conditions.*—When the lymphocyte count begins to rise after the lymphopenia, the question arises whether the increase represents a return to the general circulation of the lymphocytes formerly present that have been stored in the deep viscera (a reestablishment of equilibrium), or whether it represents the entrance of new lymphocytes into the blood from their sites of origin, or a mixture of both processes. When the number of granulocytes rises, it is known from the morphology of the cells that the marrow has been actively stimulated by the injection to discharge young cells into the blood stream. One commonly thinks of lymphocytes as being delivered into the blood stream much less readily than granulocytes. It is known that granulocytes

4. Pearce, L., and Casey, A. F.: J. Exper. Med. **52**:39 and 167, 1930.
5. Whitney, C.: Medicine **7**:1, 1928.
6. Doan, C. A.; Zerfas, L. G.; Warren, S., and Ames, O.: J. Exper. Med. **47**:403, 1928.
7. Doan, C. A.: Proc. Soc. Exper. Biol. & Med. **29**:1030, 1932.
8. Wiseman, B. K.: J. Exper. Med. **53**:499, 1931.
9. Ehrich, W.: J. Exper. Med. **49**:347 and 361, 1929.

pass directly into the venous blood stream, whereas many lymphocytes from their point of origin in the lymphoid tissue to their indirect entrance into the blood stream pass through the more slowly moving fluid of lymphatic ducts. From the experiments of Lee [10] on the cat, the indication is that roughly one half of the circulating lymphocytes reach the blood stream through the thoracic duct. From data given by Rous,[11] Bunting and Huston [12] calculated that the rate at which lymphocytes are delivered from the thoracic duct into the blood stream is 3,300,000,000 in twenty-four hours, and that after excluding entrance of lymphocytes from the spleen and the thoracic duct in the rabbit, 443,000,000 lymphocytes disappeared from the circulation in six hours. However, Ehrich [9] recently demonstrated that in hyperplastic lymph nodes resulting from staphylococcic infection in rabbits enormous numbers of lymphocytes may pass directly into the veins at the time of the greatest lymphocytosis in the peripheral blood; and it is well established that with contraction of the spleen under sympathetic stimulation or after the administration of epinephrine lymphocytes are squeezed from the pulp into the circulation in sufficient numbers to raise considerably the lymphocyte count in the peripheral blood. There is even evidence that the smooth muscle of lymph nodes contracts and causes lymphocytosis (Martin [13]).

One commonly thinks of lymphocytes as reacting to foreign substances much more slowly than granulocytes. Their locomotion is slower, and they are not phagocytic cells. The granulocytes respond rapidly in acute infections, while the lymphocytes are prominent only in the later stages of inflammation. It would, therefore, seem that in some of the experiments in which the number of lymphocytes rose so rapidly after the leukopenic period the increase was due not to any property of the cells but to the attendant physiologic factors, such as vasomotor changes, which may be responsible for these shifts.

Wiseman's [8] studies offer a possible means of determining whether the lymphocytes which appear after the leukopenic period are new or old cells. He concluded that the degree of basophilia, as observed with the staining method used by him, is a good index of the age of the cells. He divided the lymphocytes into: (1) the Y type, young lymphocytes, either small or large, the cytoplasm of which stains with the intense blue coloring of a blue glass marking pencil; (2) the M type, cells of medium age, either small or large, the cytoplasm of which stains sky blue, and (3) the O type, the oldest cells, again either small or large, the cytoplasm of which stains so faintly that it is almost colorless.

10. Lee, F. C.: J. Exper. Med. **36**:247, 1922.
11. Rous, F. P.: J. Exper. Med. **10**:238 and 329, 1908.
12. Bunting, C. H., and Huston, J.: J. Exper. Med. **33**:593, 1921.
13. Martin, H. E.: J. Physiol. **75**:113, 1932.

Under normal conditions, very few young forms appear in the circulation, and cells of medium age are slightly more numerous than the old ones. In our experiments in which this classification of lymphocytes was made (experiments 11 to 18), the fluctuations involved chiefly the M type. There is naturally considerable personal equation in classifying cells in this manner, there being marked discrepancies between records made by different persons. However, as the Y cells are the most distinctive, a significant increase in Y forms would have been the easiest to detect. Sometimes the Y forms showed a slight increase, but the fluctuations in the total lymphocyte count depended on fluctuations in the M forms (chart), and in no instance did the Y forms increase to the extent of raising significantly the preinjection level. If we grant Wiseman's conclusions that the basophilia of the cytoplasm is a good criterion of age, the results would indicate that the return rise of lymphocytes, after the lymphophenic period, is largely a rise in mature forms of medium age, which probably represents a return to the circulation of the cells which had been in circulation or reserve before the injection, and that the injected substance exerts only a slight stimulus to the discharge of new young lymphocytes. This, of course, differs from the rise in granulocytes, during which young cells are conspicuous. However, if we accept the hypothesis that the M lymphocytes not only circulate but are held in reserve in lymph tissue storage centers, their increase, taken with the slight increase of young forms, would indicate that additional cells are released; i. e., there is a process similar to that of the granulocytes.

*Effect of Splenectomy.*—In intact animals various fluctuations were observed during the leukopenic period, which were thought probably to represent a discharge of white cells into the circulation by the contraction of the spleen under sympathetic stimulation. A number of splenectomized rabbits were studied to see whether these fluctuations were eliminated. Furthermore, since it is possible that many new lymphocytes may pass directly from the spleen to the blood stream, it was determined to see whether removing the spleen altered significantly the lymphocyte counts following injection. The results indicated that removal of the spleen did not appreciably alter the cellular response to the injections.

## COMMENT

The immediate disappearance of granulocytes from a vein of the ear after intravenous injections is known to be a redistribution of cells from the periphery to the deep organs; but how this redistribution occurs is difficult to explain. One possibility is that the foreign substance is rapidly taken up by the reticulo-endothelial system and that the granulocytes accumulate in the same areas in the process of phago-

cytosing the particles. Yet the same phenomenon of redistribution occurs when the substance is not particulate matter; and the lymphocytes also, even though they do not function in phagocytosis, disappeared from the periphery in our experiments. The latter fact and the rapidity of the occurrence of the phenomenon suggest the possibility of a vasomotor change being a factor.

Camp [14] found that in rabbits the subcutaneous injection of drugs which produce an increase in tone of the sympathetic nervous system caused a decrease in the percentage of lymphocytes and an increase in the percentage of neutrophils, while drugs which produce an increase in parasympathetic tone caused a decrease in the percentage of neutrophils and an increase in the percentage of lymphocytes. Total leukocyte counts and absolute values for neutrophils and lymphocytes are not given in his paper, so it is impossible to know exactly what the changes in the blood were if the total count was changing, which is likely. The author concluded that "the distribution of leukocytes in the peripheral circulating blood of rabbits is controlled by the autonomic nervous system. The partition of leukocytes in the peripheral circulating blood is an index of autonomic balance, the lymphocytes running parallel to parasympathetic tone, and the neutrophils to sympathetic tone." It is conceivable that changes in vasomotor tone result in shifts of blood cells within the vascular system, but it is difficult to see how such changes in tone could have any selective effect on neutrophils or lymphocytes, except so far as contraction of the spleen or lymphoid tissue under sympathetic stimulation results in squeezing lymphocytes out of the pulp into the general circulation; Camp's results, however, appear to be in the opposite direction as far as can be determined without knowing the absolute values. Bueno [15] also ascribed fluctuations in the leukocyte count to changes in the balance between the sympathetic and the parasympathetic system. Sabin, Cunningham, Doan and Kindwall [16] discussed some of the older literature on the effect of the vasomotor state on leukocytes.

Mueller, Petersen and Hölscher [17] stated that intravenous injections of bacteria cause peripheral vasoconstriction and peripheral leukopenia, with simultaneous splanchnic dilatation and leukocytosis in the liver, spleen and gastro-intestinal tract. Mueller [18] expressed the belief that with intracutaneous injections also peripheral leukopenia is a vasomotor

14. Camp, W. J. R.: J. Lab. & Clin. Med. **13**:206, 1927.

15. Bueno, A. L. P.: Brazil-med. **2**:266, 1925; abstr., J. A. M. A. **86**:519, 1926.

16. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: Bull. Johns Hopkins Hosp. **37**:14, 1925.

17. Mueller, E. F.; Petersen, W. F., and Hölscher, R.: Proc. Soc. Exper. Biol. & Med. **27**:544, 1930.

18. Mueller, E. F.: Arch. Int. Med. **37**:268, 1926.

phenomenon. He maintained that this leukopenia usually affects only the granulocytes and not the lymphocytes. Again it seems difficult to conceive of a vasomotor change which could affect only one kind of white cell and not the other unless physical properties, such as adhesiveness, retain the granulocyte in the visceral blood vessels. Garrey and Butler [19] considered that fluctuations in leukocytes depending on exercise are "attributable to circulatory shifts with the liberation of leukocytes trapped in unused capillaries." Butler and Garrey [20] found that in a sympathectomized dog neither exercise, carbon dioxide nor heat caused fluctuations in leukocytes. It would be interesting to know how such an animal would respond to intravenous injections of agents ordinarily producing leukopenia.

Beard and Beard [21] found that when sodium chloride was injected intravenously leukopenia resulted, in which the fall in polymorphonuclears was striking, while the lymphocyte count sloped downward more gradually. A rapid return rise of polymorphonuclears occurred, but the lymphocytes continued to drop during the period of observation (up to three and one half hours). Elvidge [22] found that after the intravenous injection of quartz into rabbits "both polymorphs and lymphocytes take part in the leukocytosis as well as the leukopenia; the polymorphs are usually, though not always, the first to increase in number, being closely followed by the lymphocytes." After the injection of india ink, however, "the lymphocytes are the first to respond." Andrewes [23] found that after the intravenous injection of various living and dead bacteria the lymphocytes fell as well as the polymorphonuclears but not so rapidly, and that the lymphocytes might be much slower than the polymorphonuclears in rising but might eventually pass their normal limits. Wells [24] stated that after the intravenous injection of different bacteria, the lymphocytes showed no definite change during the period of polymorphonuclear fall and rise.

Doan [7] and his co-workers, after studying the effect of injections of sodium nucleinate, stated that the lymphocytes "may or may not decrease in absolute numbers during the leukopenia period." Fox and Lynch [25] in earlier experiments with dogs found that the lymphocytes as well as the granulocytes dropped after the administration of nucleic acid and of sodium nucleinate. In our experiments we invariably found that after the injection of various foreign substances a decrease in the

19. Garrey, W. S., and Butler, W. E.: Am. J. Physiol. **90**:355, 1929.
20. Butler, V., and Garrey, W. S.: Am. J. Physiol. **98**:394, 1931.
21. Beard, L. A., and Beard, J. W.: Am. J. Physiol. **85**:169, 1928.
22. Elvidge, A. R.: J. Path. & Bact. **31**:33, 1928.
23. Andrewes, F. W.: Lancet **2**:9, 1910.
24. Wells, C. W.: J. Infect. Dis. **20**:219, 1917.
25. Fox, H., and Lynch, F. S.: Am. J. M. Sc. **153**:571, 1919.

lymphocytes occurred in the peripheral blood coincident with the fall in granulocytes. If this is true, a vasomotor change must be considered as a possible factor in redistributing the cells. The fall in blood pressure noted [1] is evidence of circulatory changes.

If a vasomotor change is responsible for shifting cells from one region to another, or for changing the ratio of cells to plasma, the red cells should be simultaneously affected, and to test this point, red blood cell counts were carried out in two rabbits before and shortly after the injection of sodium nucleinate. The red cells showed some fluctuations but none commensurate with the fluctuations in the leukocytes; so it seems likely that any vasomotor changes which occur are associated phenomena and bear no causal relation to the cellular distribution. In their experiments with sodium chloride Beard and Beard found no marked fluctuations in the red cells.

Although no definite conclusions can be drawn from the experiments reported in the literature or from our own experiments, it can be tentatively suggested that any vasomotor changes are accompaniments rather than the cause of the redistribution of leukocytes after intravenous injections.

## SUMMARY

Following the intravenous injection of various foreign substances into rabbits there was an immediate decrease in the number of nongranular white cells as well as in the number of granulocytes in the peripheral blood.

Following the leukopenic period, the return rise of nongranular cells in our experiments was usually subsequent to the rise of granulocytes, and occasionally simultaneous with it.

The criteria advocated by Wiseman for gaging the maturity of lymphocytes were applied to see if they would indicate whether the lymphocytes appearing after the leukopenic period were new or old cells. Although the Y cells sometimes showed a slight increase, the fluctuations in the total lymphocyte count were dependent on the number of M cells, which probably represented a return of cells to the general circulation from temporary depots. The possibility of the entrance of reserve cells of medium age (i. e., a process similar to that of the granulocytes) is also discussed.

In these experiments splenectomy did not alter significantly the lymphocytic response.

# Laboratory Methods and Technical Notes

## NEW SIMPLE QUANTITATIVE MICROCRYSTALLOGRAPHIC ESTIMATION OF PHOSPHATES IN BLOOD SERUM

ERNEST A. PRIBRAM, M.D., CHICAGO
Professor of Bacteriology and Preventive Medicine, Loyola University School of Medicine; Pathologist, St. Elizabeth Hospital

A microcrystallographic method for the estimation of phosphates in the urine has been described in a previous article.[1] The method consists in precipitating the phosphates with an ammonium magnesium sulphate reagent (Dowd's reagent), calculating the quantity of phosphates from the type of crystals of magnesium ammonium phosphate. The attempt to apply this method to the estimation of phosphates in the blood serum did not succeed, as the crystal type formed by precipitating the serum phosphates is the lowest one (type 8 of figure 1 in the previous paper); in other words, the quantity is less than 10 mg. per hundred cubic centimeters of blood. Further dilutions do not change the type of the crystals, but make them disappear. The disappearance of the crystals has been used for a quantitative method. Certain technical conditions had to be considered, however, in making the proper dilutions. A dilution with water or with a saline solution isosmotic to the blood would change the optimum conditions for the formation of the crystals, which, as stated in the previous article, corresponds to the specific gravity of the urine. In order to secure the optimum salt concentrations the dilutions of the serum were made with a 2.5 per cent solution of sodium chloride. Furthermore, the formation of the crystals depends on the time factor. Forty-five minutes has been found empirically to be necessary for the formation of crystals in a 2.5 per cent solution of sodium chloride containing 3 mg. of phosphorus as phosphoric acid (or its salts) in 100 cc. of the fluid. Further dilutions of this fluid do not precipitate within this time.

Therefore the highest dilution of a serum made with a 2.5 per cent solution of sodium chloride which will give a type 8 crystal within forty-five minutes contains 3 mg. of phosphorus per hundred cubic centimeters of blood serum. This consideration gave the fundament for the microcrystallographic titration of the phosphate in the serum.

### METHOD

The requirements are: 0.6 cc. of the unknown blood serum; two capillary pipets holding 0.1 cc. each, graduated into 0.01 cc.; eighteen test tubes, 3 by ⅜ inches (7.6 by 0.95 cm.); Dowd's[2] reagent: magnesium sulphate, 1 ounce (28.4 Gm.); ammonium sulphate, 1 ounce (28.4 Gm.); ammonium hydroxide, 10 per cent, 1

1. Pribram, E. .: Arch. Path. **15**:213, 1933.
2. Dowd, J. H.: Illinois M. J. **56**:286, 1924.

fluid ounce (30 cc.); distilled water, 8 fluid ounces (240 cc.), and a 2.5 per cent solution of sodium chloride.

Set up two rows of tubes with nine tubes in each row. In each tube of the front row place 0.06 cc. of serum; to the second tube of this row add 0.01 cc. of the 2.5 per cent solution of sodium chloride; to the third, 0.02 cc.; to the fourth, 0.03 cc., etc., increasing by 0.01 cc. the contents of each of the remaining tubes. Mix well and transfer exactly 0.05 cc. of the diluted serums to the corresponding tube in the second row. To this 0.05 cc. add 0.01 cc. of Dowd's solution and mix immediately. Let the mixture stand for forty-five minutes and examine it for crystals. The last tube containing crystals contains 3 mg. of phosphorus per hundred cubic centimeters. Determine the total amount of phosphorus in the serum by means of the following tabulation:

| Last Tube Containing Crystals | Mg. of Phosphorus per 100 Cc. |
|---|---|
| 9 | 7 |
| 8 | 6.5 |
| 7 | 6 |
| 6 | 5.5 |
| 5 | 5 |
| 4 | 4.5 |
| 3 | 4 |
| 2 | 3.5 |
| 1 | 3 |

Comparison of this method with the colorimetric method showed that the colorimetric method gave 4.2 mg. in 100 cc. of serum, and the microcrystallograhpic method, 4 mg. in 100 cc. of serum. The difference of 0.2 mg. per hundred cubic centimeters is caused by the difference in the two methods, as the intervals used in the dilutions of the microcrystallographic method do not allow the estimation of less than 0.5 mg. per hundred cubic centimeters. These differences, however, are within physiologic limits.

The practical application of the method will be described in further articles.

## SUMMARY

The precipitation of phosphates by means of a proper ammonium magnesium sulphate reagent (Dowd's reagent) can be used for a quantitative estimation of the phosphates in the blood serum. Equal quantities of serum, diluted with increasing amounts of a 2.5 per cent solution of sodium chloride, are precipitated with the reagent; the last tube in which the crystals are found within forty-five minutes contains 3 mg. of phosphorus in 100 cc. of serum. The percentage of serum phosphates is calculated from the dilution.

# General Review

## HODGKIN'S DISEASE

ANDREW WALLHAUSER, M.D.
PITTSBURGH

A century ago Thomas Hodgkin presented 7 cases of a peculiar lymphadenopathy with anemia, and so called attention to the obscure disease that bears his name. Despite the uncertainty as to the true nature of the disease, much has been accomplished in these years; this review is presented in order to sum up and to correlate as far as possible the accumulated literature. It has been compiled rather as a supplement to, or a continuation of, several outstanding reviews and monographs than as a complete survey of the subject.

### NOMENCLATURE

Perhaps no other disease has been encumbered with a more surprising array of names than has Hodgkin's disease. Even special features, such as those of symptomatology, pathology and histology, are presented by the various writers under a terminology which seems to vary according to individual preference or invention. Such a state of affairs is deplorable and has made progress more difficult than it need be. In order to call attention to this situation, the following designations were extracted from the literature; direct translations into other languages of several of the more common names are not included:

Hodgkin's disease, Reed-Hodgkin's disease, Pel-Ebstein disease, Paltauf-Sternberg's disease, maladie de Hodgkin-Paltauf-Sternberg, Sternberg's disease, Hodgkin-Wilks' disease, multiple lymphoma, malignant lymphoma, Hodgkin's granulomatous lymphoma, lymphomatosis granulomatosa, chronic lymphomatosis, chronic malign lymphomatosis, chronic benign lymphomatosis, malignant infectious granuloma, Hodgkin's granuloma, granulomatosis, granulomatosis textus lymphatice, malignant granuloma, Sternberg's malignant granuloma, das chronische Rückfallsfieber, progressive lymph node hypertrophy, lymphogranuloma, lymphogranulome tuberculeux, malignant lymphogranuloma, lymphogranulomatosis spleno-meseraica, lymphogranulomatosis, eosinophilic lymphogranulomatosis, lymphogranulomatosis perniciosa, lymphogranuloma of the Hodgkin type, lymphogranulomatosis Paltauf-Sternberg, lymphadenoma, lymphadenome métatypique, adénie, adenomycosis, adénite prurigène éosinophile, anemia lymphatica, anemia splenica, pseudoleukemia, multiple lymphadenome ohne leukemia, infectious form of pseudo-leukemia, acute pseudo-leucocythaemia, cachexia sans leucémie, aleukemic malignant lymphoma,

From the Pathological Laboratories, University of Pittsburgh.

lymphoblastoma, lymphoblastoma of the Hodgkin type, scirrhous lymphoblastoma, lymphosarcoma of the Hodgkin type, desmoid carcinom, malignes Lympho-Sarcom, megakaryoblastoma.

I wish to enter a protest against certain tendencies in nomenclature which are apparently on the increase. Since the etiology, or even the exact status of the disease is not known, it can but add to the confusion if cases, and especially series of cases, are described under titles which may perhaps express the respective writers' individual ideas, but which have not been generally accepted. Valuable statistics are buried, often beyond reclaim, under the name "lymphoblastoma," which includes a whole list of pathologic conditions; the term "lymphogranuloma" is incorrect in many cases, for it does not include all of the possibilities, and other names have similar defects. It would seem to be preferable to retain the older name of "Hodgkin's disease," or possibly the widely recognized term of "lymphogranuloma," at least until the actual status and etiology of the condition are shown. The latter term is conveniently abbreviated to "Lg," especially by European authors.

## INCIDENCE

Symmers, in a review of 8,485 general autopsies performed at Bellevue Hospital, New York, during fifteen years, collected 14 cases of lymphogranuloma, representing 0.16 per cent. Barron, reviewing 7,253 general autopsies, found 24 cases, 0.32 per cent. These two analyses combined give the following result: among 15,783 cases of disease in general there were 38 of lymphogranuloma, or 0.24 per cent. Pack and Le Fevre found records of 335 cases in the Memorial Hospital, New York, which represented 1.75 per cent of all admissions. As this hospital has a very extensive service for the treatment of patients with tumors, the incidence is higher than the average, which might be considered as considerably less than 1 per cent of all deaths.

Brandt (Latvia), Harbitz (Norway), DeJong and others believed the disease to be increasing. In the discussion of Aubertin and Destouche's paper, the consensus was that the disease has increased in frequency since the World War; Rist made the point that biopsies are now more generally used in diagnosis, and hence, the supposed increase. Fox believed essentially the same thing. Fox and Farley, in 1922, noted that diseases of the lymph nodes with enlargement and without an increase of leukocytes in the blood had become more frequent in recent years. Much, of course, is to be said for the general trend toward more accurate diagnosis by biopsy. It is astonishing, however, how frequently cases are reported with a diagnosis of lymphogranuloma in which no microscopic studies were made, in spite of the universal recognition of biopsy as a requisite for the diagnosis of this condition.

### DURATION

This phase has been rather well covered by numerous authors. I hesitate to generalize as to the duration of the disease, believing that each case is affected by so many different factors that such statistical handling might tend to obscure rather than to clarify. Burnam mentioned treatment, hard work, poor food and intercurrent infections as important influencing factors. To these may be added the age at onset, the disease being more malignant in children than in adults (Ziegler, Borsutsky, Fabian), and also the fact, as stated by Terplan and Mittelbach, that in young adults the course is more apt to be chronic. Rolleston cited the case of Brunner's patient who died after but two weeks of symptoms suggesting cardiac failure, the autopsy revealing extensive lymphogranulomatosis; this case is thought-provoking when one considers others of apparently short duration, for the disease had possibly been under way for a much longer time. Other cases of short duration were reported by Weber and Bode (eleven weeks); Ziegler (one month) and Barron (two months). I observed a case in which the patient survived only seven weeks after the apparent onset.

The average duration from onset to death, according to various observers, is as follows (stated in months): Cunningham, thirty-six; Desjardins and Ford, thirty-one; Burnam, twenty-four; Longcope and McAlpin, twenty-four; Simmons and Benet, twenty-four; Vasiliu and Goia, thirty; Klewitz and Lullies, twenty; Blackford, thirty-six and six tenths; Barron, seventeen; Wellbrock and Loughery, thirty-one; Corbeille, twenty-two and five-tenths (children); Borsutzky, twenty-two (children); Acuña and Casaubón, twenty (children). The duration in the series of cases in children shows remarkable agreement.

MacNalty stated that the duration tends to be more prolonged in cases involving the superficial nodes than in those in which the internal nodes alone are involved. Blackford, in discussing Muller and Boles' paper, felt that cases might be divided into two classes as to duration and course: (1) those in which the patients died within two years and (2) those in which the patients, surviving this apparently critical period, lived more than six years. This dividing line he believed to be quite sharp. Cunningham stated: "The prognosis of longevity in Hodgkin's disease is an uncertain factor even when there is an extensive involvement." He estimated the average duration as three years but cited a case in which the patient lived twenty-five years.

Regarding the influence of treatment on duration, there is again a variety of opinion. It will be preferable to discuss this aspect under treatment.

After analysis of a large number of cases, the average duration is estimated at about twenty-four months, tending to be more than two years rather than less.

### SEX

Several authors have given the ratio of male to female patients. The following figures represent a compilation from twenty-one publications, with mention of a total of 1,447 patients, 1,009 males, and 438 females. The ratio of males to females is 2.3: 1. This ratio appears to be well established, and it is believed that it represents a rather true value, supplanting ratios based on a much smaller number of patients. The ratio is even more striking in children 15 years of age or less: total patients, 77; male, 64; female, 16; ratio of male to female, 4: 1.

The significance of these figures cannot, of course, be settled at this time. That there is a definite preponderance of male patients is apparent. Bunting has already stated that "age and sex importantly influence the susceptibility of the lymphoid tissue to disease," and that they also play a part in the rate of progress of the disease process. Gemmell, in a study of 57 cases in females, came to some highly interesting and original conclusions. He believed that the female has more protection against the disease than has the male, and he indicated the ovary as the seat of such protection. He therefore concluded that "as long as there is sufficient ovarian hormone in the general circulation, the individual can resist the disease," and that "possibly Hodgkin's disease occurs, in the female, chiefly when there is a hypo-function of the ovary."

### AGE

There are numerous figures in the literature regarding the ages of patients. Unfortunately, few writers state whether the age represents the time of onset, of the first consultation or of death. Such knowledge is, of course, indispensable in a statistical study. However, with the available data, the following facts seem reasonably well established. The disease occurs most frequently in young adults (from 18 to 38 years), but may occur in persons of any age. The youngest patient whose case is recorded was the child observed by Priesel and Winkelbauer, who was 4½ months old at death and apparently was born with the disease. Wollstein and McLean reported a case of thymic Hodgkin's disease in a child 4½ months, and Pinelli, a case in a child of 6 months.

Corbeille noted that more than half of the cases occurring in children begin during the first five years of life. After a study of the literature, as well as observation of personal cases, I feel that this is true. Furthermore, it is surprising how few of the cases occur at the period of puberty. Of 33 cases in children 15 years old or younger, only 2 occurred between the ages of 12 and 14. The drop in the curve is remarkable. I recognize, of course, that puberty occurs at different ages in different persons.

It is my opinion that both sex and age are definitely involved in this disease.

HISTOLOGY

The historical aspects are interesting. The earliest description of "lymphadenoma cells" was that by Virchow, in 1864; Langhans, in 1872, described giant cells in lymphogranuloma. In 1878, Greenfield noted and drew large multinuclear cells but did not go further, although he had unquestionably discovered the distinctive histologic picture. Goldmann, in 1892, pointed out the frequency of local eosinophilia in the nodes. Sternberg, in 1898, described the characteristic cell which bears his name and laid the foundations for the histologic recognition of the disease. Andrewes, simultaneously with Reed, in 1902, gave the first full description of the histologic appearances. It is well known that Hodgkin's original 7 cases described in 1832 were not all instances of true lymphogranuloma. Fox examined the data on these cases, finding only 3 in which he could consider the condition to be lymphogranuloma as it is known today. In the remaining cases the disease was tuberculosis, syphilis or leukemia. Furthermore, of Wilk's 13 cases, Fox considered only 5 as instances of true lymphogranuloma.

The classic histologic process of Hodgkin's disease is generally described as a progressive diffuse granulomatous (or neoplastic) process, beginning with lymphoid hyperplasia of the lymph nodes, gradual loss of the normal architecture and its replacement with a polymorphocellular tissue, and terminating with the formation of hyaline fibrous tissue. In addition, variations in this general picture are recognized, especially in atypical and borderline cases, in which diagnosis may be difficult or even impossible.

The first histologic change observed is a proliferation of the cells covering the reticulum of the sinuses and of those of the germinal centers (Reed; Simmons), formation of nodules by proliferation of the endothelium of the lymph channels and the capillaries (Sternberg; Coronini) or hyperplasia of the lymphoid cells and of the cells of the germinal centers (Longcope; Fabian; Lemon and Doyle; Symmers). Terplan and Mittelbach did not consider lymphocytic hyperplasia a feature of typical lymphogranuloma, and they called attention to the overgrowth of reticulum cells in the earlier stages.

The ensuing progressive changes appear to vary not only in different nodes but in the elements composing the nodes, according to different investigators. These changes, however, consist in replacement of the normal lymph node structure by a polymorphocellular tissue composed of varying quantities of lymphocytes, endothelial cells, eosinophils, polymorphonuclears, plasma cells, fibroblasts, reticulum, epithelioid cells, megakaryocytes, Langhans' giant cells, myelocytes, myeloplaxes and Sternberg-Reed cells (or lymphoblasts). Certain of these may preponderate, giving more of a sarcomatous picture; in other cases the

cellularity may be greatly decreased, the picture being that of fibrous tissue with a few scattered polymorphic cell nests. The latter appearance is commonly ascribed to the last stage of the disease. Any or all of these pictures may be present in a single node or chain of nodes, which is a point of practical diagnostic importance. Cunningham advised the resection of several nodes in order to avoid confusion in histologic study and diagnosis. Barron also emphasized this. The cases of Sabrazès illustrate the occurrence of mixed histologic pictures.

Before considering several of the more detailed phases, it may be well to review the modern aspects of histologic diagnosis. The criteria necessary to establish a diagnosis of Hodgkin's disease are hardly standardized or uniform, and the apparently increasing inclination of some writers to submerge all or many neoplastic or neoplasmoid structures of lymphoid origin under the enveloping and unqualified term "lymphoblastoma" has further complicated the problem.

In the earlier, immature stages of the disease diagnosis may be impossible, as there is nothing entirely characteristic. Later, after the appearance of the polymorphocellular picture, it may be easy. Twort emphasized that the presence of "lymphadenoma cells" (Sternberg-Reed cells) is always necessary for a certain diagnosis, and that with mitoses in several kinds of cells, débris necrosis of a particular type, the presence of eosinophils and general loss of architecture are strong supporting points. He stated that mitotic figures in endothelial cells are of great importance, as it is exceptional to find them in chronic lymphadenitis; the same is true of mitoses in fibroblasts and lymphocytes. The usual mitotic figure in lymphogranuloma is like an irregular bundle in the center of the dividing cell; this distinguishes the condition from lymphosarcoma, in which the figures are club-shaped. No single feature can be used as a criterion for certain diagnosis. Sternberg recently stated his concept of the histologic picture—a polymorphocellular granulation tissue, containing lymphocytes, plasma cells, epithelioid cells, frequently eosinophils and especially the large mononuclear or multinuclear cells with abundant cytoplasm and large round, oval or variously shaped, darkly staining nuclei, either lobate or not, and darkly staining. He held that the diagnosis cannot be made without the presence of these cells. He also considered characteristic a regressive tendency of the granulation tissue, with focal necrosis and areas of fibrosis or hyalin. L'Esperance's basis for diagnosis consists in the presence of peculiar myeloid giant cells, endothelial cells, lymphocytes and fibrosis. Hansmann gave particular attention to the filling in of the hilus with solid lymphoid tissue, destruction of the architecture and obscuring of the reticulum of the lymph nodes. "This leaves a lymphomatous mass without any regard for physiologic function in the arrangement of the lymphoid element." Both gross and microscopic studies are

necessary. Hansmann found the well formed Sternberg giant cell frequently lacking. Mallory and other exponents of the lymphoblastic nature of the disease naturally insisted on the presence of the lymphoblast (Sternberg-Reed cell); these cells may be many or few, but they are always present in affected nodes. Medlar, in offering his theory as to the megakaryoblastomatous nature of the disease, expressed the belief that "it is essential to have a pleomorphism of cells which represent the developmental cycle of the megakaryocyte" and that neutrophilic or eosinophilic infiltration or fibrosis is not necessary for a positive diagnosis. Vasiliu and Goia found the Sternberg cell indispensable in making the diagnosis. These cells are not constant in all foci and may be lacking in many. Sweany based the diagnosis on "the gradual spreading type of lymph node tumor that reveals microscopically: diffuse hyperplasia of the lymph node reticulum with varying numbers of bone marrow type of giant cells, and similar types of cells in liver, spleen or lung metastases (when present)."

Boyd pointed out that the picture varies according to the stage of the disease but that ultimately the characteristic changes are seen. Following an early lymphoid hyperplasia, there is replacement by a proliferation of reticulo-endothelium, with the formation of masses of pale cells with pale vesicular nuclei. In addition, there are the lymphadenoma cells (of Reed), which are described as large cells having from four to ten crowded nuclei with dark nucleoli. Eosinophils are rarely absent and "in none of the other pathological conditions affecting the lymph glands are they present in any numbers." Fibrosis may or may not be present. McJunkin held that large mononuclear and multinuclear cells, with vesicular nuclei containing one or more nucleoli, are the characteristic histologic feature. Power and Hala described the usual pleomorphism, but stated that endothelial hyperplasia is invariably absent.

Occasionally the diagnosis "atypical Hodgkin's disease" is encountered, both in the literature and in practice. Under this uncertain designation are placed various unrecognizable conditions, lesions of the lymph nodes that do not fall easily into any other diagnosis and a few cases of true Hodgkin's disease with unusual histologic features. Sternberg recently considered this important question and maintained that in this use of the term physicians have actually gone backward in their knowledge. He further criticized the occasional tendency to arrive at a diagnosis "by exclusion." Abrikossoff called attention to the same trend.

The occasional similarity of Hodgkin's disease to other conditions will continue to cause confusion until the etiology of the disease has been demonstrated. Mention of this problem has been made with

reference to chronic hyperplastic tuberculosis (Karsner), certain thymomas (Ewing), nodes in glandular fever (Baldridge, Rohner and Hansmann; Sprunt and Evans; Longcope), hyperplastic chronic lymphadenitis (Terplan and Mittelbach) and hyperplasia of the giant lymph follicles (Brill, Baehr and Rosenthal). Karsner commented on a form of lymphatic tuberculosis which produces a histologic picture much like that of Hodgkin's disease, but is separable by careful examination; he suggested that this may have caused confusion in those cases which appeared to confirm Sternberg's findings. Metastatic carcinoma may occasionally produce a curious reaction which for a time at least closely simulates Hodgkin's disease. In conclusion of this all too brief discussion of atypical lymphogranuloma, it may be helpful to quote from Sternberg: "The diagnosis of atypical lymphogranuloma has come to mean about as much as pseudoleukemia, into which everything was placed that did not fit elsewhere. This is a pitiable back-step."

The reticulum was studied by Foot, who found the amount variable. In some nodes there is a great deal of new reticulum, and in others practically none. It is usually borrowed from the native tissue of the invaded node and becomes transformed into collagenous tissue. The reticulum in Hodgkin's disease behaves as one would expect it to do in a granuloma rather than as in a tumor.

The reticulo-endothelial system has been prominently mentioned in relation to Hodgkin's disease, especially by Piney, who called the disease a reticulo-endotheliosis. Jaffé found the epithelioid cells of lymphogranuloma similar to those of tuberculosis (Doan and Sabin). McJunkin traced the Sternberg-Reed cells to the reticulum cells. The relationship can hardly be considered as established at the present time.

Vital and supravital staining have been tried. McJunkin stated that reticulo-endothelial cells react characteristically with neutral red, forming spherical aggregations of the dye in the cytoplasm. From the results of injections into lymphogranulomatous lymph nodes he concluded that the Sternberg-Reed cells are derived from reticulo-endothelium. He further stated that "the large hyperchromatic nucleus with a relatively small cytoplasmic mass of dye granules points to a local multiplication by mitosis which is rapid in comparison with that of the same kind of cell in epithelioid tubercles."

Sabin stated that nodes from early cases, when stained supravitally, show many epithelioid cells characteristic of those found in tuberculosis. Fox found a certain number of rosette cells in nodes stained with neutral red (intravital stain). Janus green showed no structures comparable to mitochondria. Injections of lampblack showed no specific cellular ingestion. Latta and Schulz described the reactions of lymph nodes in general to intravital staining. Laidlaw offered a method for

differential staining of ectodermic and mesodermic cells by silver and described the reaction of the Reed cell in Hodgkin's disease.

The experimental production of the typical histologic picture of lymphogranuloma has not been accomplished, although some writers have described reactions more or less closely approximating it. Bunting and Yates believed that they had reproduced the lesion by the injection of their diphtheroid bacillus. Grumbach described reactions from the use of benzene and of tar. Partial reproductions, such as the development of cells resembling those of Hodgkin's disease, have been described in several papers (Benzançon, Weissmann-Netter, Oumansky and Delarue).

Freifeld described an unusual lipoid cell hyperplasia in lymphogranuloma—peculiar groups of light, foamy cells embedded in typical lymphogranulomatous tissue, suggesting a localized xanthomatosis and a possible relationship to Niemann-Pick and Gaucher diseases. Sternberg criticized the diagnosis in his paper on atypical lymphogranuloma.

Invasion of the capsule has been described thoroughly (MacCallum) and may be taken as a fact. Reed did not at first believe in this.

The occurrence of Charcot-Leyden crystals may be marked at times, according to Nicol. Simonds suggested that their presence is related to the local eosinophilic infiltration. Ziegler found the crystals in fresh tissue. Mayr and Moncorps, by a special technic, demonstrated them in suspensions of normal eosinophils.

Necrosis is reported both as frequent (Kusunoki) and as rare (Cunningham). It differs from the necrosis of tuberculosis in that the dead tissue retains its essential structure (Kraus, Lubarsch). Andrewes, as well as Yates and Bunting, believe that it indicates a secondary infective process. Cunningham commented on the association of areas of necrosis and possible anaphylactic phenomena, citing the work of Blumer, who caused lymphatic necrosis in guinea-pigs by the injection of emulsions of nodes from a case of status lymphaticus, and also the work of Woltman, who obtained similar effects by injections of foreign serum. Bierich, Galloway and Urchs suggested that "resorption of partially disintegrated protein from these areas of necrosis may give rise to anaphylactic phenomena." Interference with the local circulation by granulomatous involvement represents the views of Hauck, Chiari and Tsunoda. Twort cited 17 of 61 cases as showing débris necrosis.

The effects of radiation therapy on the histologic picture of lymph nodes were considered in some detail by Fox and Farley, who gave a general summary of the pioneer work by Heineke, Pusey and Senn, and Warthin and the confirmation and amplification by David and Desplats, Pancoast, Clarke, Murphy and others. Briefly summarized, the findings are: After irradiation changes may be perceptible almost immediately in the blood, but they are best seen in the glands after

several days. Mild doses produce a low grade hyperplasia in the cords and follicles, while larger doses or repeated exposures are followed by diminution of the number of small mononuclears. After repeated doses large cells resembling lymphoblasts appear. If the irradiation of normal nodes is not too prolonged, the normal architecture returns, but this is not so in the case of pathologic nodes. The reactive phenomena may be stated as an increase in lymphoblasts and endothelial and fibrous tissue. In Hodgkin's disease in particular, there is extensive disappearance of mononuclears, with fibrosis and a reduction in the number of lymphocytes. The tuberculous and the Hodgkin type of granulomatosis belong together, reacting to roentgen irradiation differently from the leukemic and neoplastic hyperplasias. "Tumor cells degenerate readily and completely alter their shape, while lymphoblastic cells retain nearly normal proportions and may vary little or none in staining qualities." Nakahara described the changes in lymphoid organs after roentgen treatment. Isaacs found that myeloblasts and lymphoblasts were stimulated. Simmons and Benet could find no change due to radiation therapy.

The subject of eosinophilia of the nodes has been covered by numerous writers. Goldmann, in 1892, first noted eosinophils; he believed them to have been withdrawn from the blood, a view more recently stated by Symmers. The latter believed that the etiologic agent reacts on the marrow, giving rise to the proliferation of lymphoid type cells, eosinophils and eosinophilic myeloplaxes. These reach the nodes via the blood stream. Barron felt that the presence of eosinophils in the nodes is probably coincident with an eosinophilia of the blood stream. Montgomery suggested the possible significance of eosinophilia in tissue as pointing to involvement of bone. Regarding its value in diagnosis, opinion is divided, and as Simonds stated, "Düring's view is a reasonable one to adopt, namely, that while eosinophiles are not peculiar to Hodgkin's disease, there is no other condition in which they are found in such numbers." The general aspects of eosinophils and immunity are covered by Hajós, Woltman and Ringoen. General articles of value include those of Maximov, Downey and Simonds.

Giant cells in lymphogranuloma have been variously described and named. As already stated, Virchow, in 1864, noted large, peculiar cells, that were later strongly emphasized by Sternberg, in 1898, and by Andrewes and by Reed, in 1902, as of prime importance in the specific picture.

Vasiliu and Goia classified the Sternberg cells into at least two types—the plasmocytic and the reticulo-endothelial varieties. The plasmocytic type is characterized by a clear vesicular nucleus, poor in chromatin, with a large nucleolus (the illustrations show a close resemblance to the typical Sternberg-Reed cell). The reticulo-endothelial type

resembles a multinucleated reticulo-endothelial cell (the illustrations show some resemblance to the megakaryocyte). In the plasmocytic type, all transitions from the plasmocyte to the Sternberg cell may be seen. These authors also noted megakaryocytes and myeloplaxes of the bone marrow type. Carballo described a case of a sarcoma-like, plasma cell lymphogranuloma with a large plasma cell as the predominating type. Lange believed that the Sternberg cell arises from the adventitia, a view held by numerous others (Catsaras-Georgantas; Kirchner; Terplan; Russell; Warneke; Marchand). Mallory's well known view that this cell is a lymphoblast is, of course, held by those who feel that the disease is a lymphoblastoma. Medlar suggested the possibility of the identity of the Sternberg cell and the megakaryocyte, and this forms the basis for his theory of the megakaryoblastomatous nature of the disease. Medlar's views are possibly the most recent development in the field of the probable nature of the disease.

In studying the literature on the Sternberg cell, also called the Dorothy Reed cell, rather different descriptions were encountered, which are not easily reconciled. The cell described in Sternberg's original paper, in 1898, has abundant cytoplasm and one or more large, variously shaped nuclei which stain intensely. His illustrations clearly show this form. Reed's description and illustrations are different. She depicted a large cell with a large pale nucleus or nuclei showing a prominent chromatin network and prominent nucleoli that take a contrasting stain. The cytoplasm shows irregular protoplasmic processes. The question as to the relationship of these cells remains unsettled, but certainly the two descriptions would indicate the existence of two types of the so-called specific giant cells. Cases are continually encountered that show a preponderance of one or the other of these types. Haythorn, Robinson and Johnson described a case of Hodgkin's disease in which the patient was secondarily infected with a monilia. The reaction in the areas infected with the monila as well as in the Hodgkin's nodes showed typical Dorothy Reed cells, and this suggested that "these cells are wandering cells which may respond to inflammatory stimuli outside of the Hodgkin's nodules, just as other wandering cells and blood elements are capable of doing."

Giant cells of the Langhans type are mentioned by several authors (Reed; Karsner; Longcope). Karsner differentiated the giant cells of hyperplastic tuberculous lymphadenitis from those seen in Hodgkin's disease in that "the former show relatively solid nuclei, and the latter distinctly vesicular nuclei." Haythorn, in an extensive review of multinucleated giant cells, considered both the Reed type and the foreign body type. He stated that the two are apparently constantly associated in Hodgkin's disease as well as in lymphoblastic tumors, but are not related in origin.

Goldmann described "Kugelzellen" in Hodgkin's disease, and these were considered by Reed. With Ehrlich's tri-acid stain they appear as large cells with a golden-red cytoplasm made up of large, irregular droplets with a small, indefinite nucleus. Carballo reported on the occurence of pleokaryocytes (hyperlobulated forms of polymorphonuclears), stating that he found them locally but not in the peripheral blood.

Finally, the megakaryocyte, to which Medlar called attention, must be considered. Reference to Medlar's original paper should be made for the details of his views on the megakaryocyte and its ancestors. Meyer stated that megakaryocytes exist in normal lymph nodes, more profusely in the fetus than in the adult human being. Aschoff said that their naked nuclei are frequently lodged in the capillaries of the lungs. Minot held that these cells usually block the further passage of the normal megakaryocytes and that consequently those seen in the peripheral circulation are most commonly fragments or nuclei. Watson discussed their presence in the blood, the spleen and the liver in a case of splenomegaly with anemia. Körner and Minot described cases of myelogenous leukemia with numerous megakaryocytes.

## GENERAL BLOOD PICTURE

Attempts to formulate hematologic criteria for the positive diagnosis of Hodgkin's disease have not been successful. Bunting claimed that such a diagnosis is possible, and he has made it on several occasions (Yates). McAlpin could not substantiate these claims, and most observers have agreed that the findings are neither typical nor constant.

Unfortunately, in many cases there is only a single blood count, taken at random. Fabian, in 1911, insisted on numerous counts. Bunting used counts based on at least 500 cells and made them himself, feeling perhaps that the average technician is hardly qualified to make the exact determinations necessary or to gain the mental impression that only a personal and expert examination gives.

It is hardly necessary to refer to the changeable clinical course, the profound effects of radiation therapy, the effects of diet and metabolism, the influence of localization, especially regarding the hematopoietic system, and the possibility of secondary infections. All of these and more must be considered in relation to the blood picture and its interpretation.

There seems to be a definite trend toward attempts to obtain type blood formulas in relation to preponderating localization and course. Thus Favre associated pruritus with eosinophilia. Hayden and Apfelbach reported that in cases involving the gastro-intestinal tract there was generally a normal or a low white cell count in the presence of fever,

secondary anemia, actual lymphopenia or slight eosinophilia. When the spleen was affected, Rolleston and also Weber found leukopenia with lymphocytosis. Weber also suggested that in cases of very high eosinophilia the intestine was invariably involved. Eosinophilia as a specific reaction of the bone marrow was noted by Stewart. Montgomery's work was in agreement with this; he suggested a search for involvement of bone in the presence of definite eosinophilia.

Barron suggested the possibility of confusion of Hodgkin's disease with typhoid or with relapsing fever in the presence of leukopenia in the more acute cases with prolonged high fever. The similarity is close, especially in cases without externally visible lymphadenopathy. Numerous observers have made use of the blood count in differential diagnosis, especially in relation to the leukemias; this is a finding of value.

The following opinions as to the general findings in the blood are briefly abstracted: Bunting noted in cases of less than one year's duration that there was no leukocytosis but that relative lymphocytosis occurred, as well as an increase in transitionals and a decrease in eosinophils. McAlpin could not confirm this, but Falconer did, adding that later in the course there may be leukocytosis, with polynucleosis, a fairly constant mononucleosis, no elevation of the platelet count, and an eosinophil count usually about normal or lower, but occasionally very high. Muller and Boles noted an early lymphocytosis followed by polynucleosis and an increase in transitional cells and platelets (findings which in general agreed with those of Bunting). Fox found polynucleosis, a normal lymphocyte count, early anemia and a chronic course. Schreiner and Mattick noted secondary anemia, leukocytosis, polynucleosis, moderate eosinophilia and an increased platelet count, an increase in the transitional cells not being commonly present. Straube reviewed the literature and contributed 21 cases of his own. He held that there is no uniform and specific blood picture, and that the condition cannot be diagnosed on the basis of the findings in the blood.

The most common and constant finding seems to be a relative and absolute moderate polynucleosis with lymphopenia. Aubertin in 100 observations found this lacking but 9 times, and he considered leukopenia absolutely exceptional when radiation therapy has not been used. Vasiliu and Goia reported that an elevated leukocyte count may indicate a malignant trend. Baldridge and Awe believed the sclerosing type of lymphoma to be the most frequent cause of a nonleukemic leukocyte count of 20,000 or more in a patient free from fever. Bunting and Yates have long held that leukocytosis occurs later in the course. Rolleston did not find leukocytosis, but rather a normal count or leukopenia. Klima studied 32 cases and came to the conclusion that in the early stages or in remissions the count was normal; in chronic generalized

lymphogranuloma or when tumor-like masses were present, there was an increase in neutrophils and monocytes or a progressive lymphopenia, and rarely eosinophilia; the red cells were normal or moderately decreased in number; in the rapidly progressing cases, there were severe anemia, neutropenia and progressive lymphopenia or eosinophilia, and marked lymphopenia seemed to be a sign of a rapid course.

Leukopenia may be very marked (Gütig; Meyer; Mellon; Urchs; Jaffé; Miller). Miller cited a case in which the leukocyte count was only 240. Moderate leukopenia (a count below 6,000) was reported in a small percentage of cases (Ziegler; Fabian; Barron; Miller [who also gave a special bibliography]). Simmons and Benet never found leukopenia. Weber reported that it is not uncommon in the advanced stages of the disease. Bine described progressive leukopenia. Fox and Farley also discussed leukopenia. The leukocyte count may be normal, not only at odd times but during the entire course of the disease (Miller; Fabian; Ziegler).

The leukocyte count may be oscillating. Thomson described a remarkable daily fluctuation of from 6,000 to 75,000. Another case of his showed a variation of from 6,000 to 66,000 in twenty-four hours. In a case of cancer he found a daily variation of from 5,000 to 40,000. Simmons and Benet cited a case in which the percentages of polymorphonuclears and lymphocytes were reversed. Fabian's insistence on repeated counts hardly need be emphasized under these conditions.

*Hematologic Effects of Irradiation.*—As the roentgen rays have played so extensive a part in the therapy of this disease, and as their effects are profound, not only on the actual lesions but on the general organism, it is important to consider the blood picture as it is affected in the course of such treatment. Minot and Spurling investigated this subject extensively with human and animal blood and found that exposures to roentgen rays of short wavelength produce a definite and somewhat persistent leukopenia, which is in proportion to the dose used. "Coincident with the drop in the lymphocytes, the polymorphonuclear eosinophiles undergo a decrease—later they may increase over a period of days to weeks, reaching often above normal and sometimes as high as 15 per cent, then returning to normal in a similar period of time." They summed up the usual course of events as: (1) transient leukocytosis; (2) leukopenia lasting from nine days to four weeks, with lymphopenia, the leukocyte count being still further depressed if treatment is given before the return to normal; (3) eosinophilia, with a count of from 7 to 23 per cent, from two to three weeks after exposure; (4) the appearance of degenerated cells, especially during the first three days; (5) a slight increase in platelets.

Fox studied the influence of the roentgen rays on the polymorphonuclear count: These cells were increased and were not influenced

by roentgen irradiation, whereas in the leukemic group the polymorphonuclears were few and were sensitive to the roentgen rays.

The peculiar sensitiveness of lymphoid cells to the roentgen rays was first brought out by Heineke. Taylor, Witherbee and Murphy studied the effects of roentgen irradiation on several types of animals and found that there is a sharp fall in the lymphocyte count during the first two days, followed by a slight rise and then another slight fall which is followed by a final rise. They also found that in 7 of 9 rabbits lymphocytosis could be produced by small doses of roentgen rays. Portis, examining the blood picture shown by workers with x-rays, found leukopenia with lymphocytosis and occasional myelocytes. No change was noted in the red blood cells and platelets. These results appear to be in accord with those of Taylor and his associates.

Isaacs considered the mechanism involved in the roentgen treatment of leukemias and lymphomas. He stated that the roentgen rays stimulate primitive myeloblasts and lymphoblasts to rapid reproduction. Myelocytes and small lymphocytes are stimulated to finish their life history; they then die or are excreted, very rapid excretion resulting in a leukopenia which gives the false impression of an aplastic bone marrow. Anemia may mean crowding out of the red blood cells by foreign cells, or it may mean actual aplasia of the marrow.

Shawhan discussed the hematologic response to irradiation in a case of Hodgkin's disease; he found essentially a return to a much more normal count than was shown before treatment. Burnam noted the same in many cases. Simmons and Benet have noted that radium treatment reduces the lymphocyte count in Hodgkin's disease, the maximum effect being seen in about two weeks. Krantz agreed. Weber called attention to the possible influence of prolonged roentgen therapy in producing a lowered polymorphonuclear count and anemia.

In summary, the blood picture in a case of Hodgkin's disease in which radiation therapy is used will depend not only on the disease process itself but on the several factors involved in the effects of radiation therapy. This must be held in mind in attempting any evaluation of the blood count in this disease.

*Erythrocytes and Hemoglobin.*—Moderate progressive anemia of the secondary type is the rule, the degree varying in different cases. Piney stated that "the absence of any great degree of interference with erythropoiesis is to be expected in a malady in which the essential feature is formation of hyperplastic reticuloendothelium, which is an extra- rather than an intra-vascular process." Barron described the anemia as of the cachectic type and present in all cases in the last stages, though it may occur early. The hemoglobin averaged from 30 to 60 per cent; in one case it was but 19 per cent. Burnam stated that

the anemia is usually not profound, the average hemoglobin value being about 70 per cent, and that poikilocytosis, polychromatophilia and nucleated red cells are exceptional. Straube attached small importance to the anemia. Halix stated, however, that early in the course there may be severe anemia, which may closely resemble pernicious anemia. Piney stated that at times erythroblasts appear in small numbers; their occurrence is common in advanced cases involving the bone marrow. Borsutzky found severe secondary anemia in all cases in children. He observed no hemorrhagic diathesis in children. Baldridge and Awe cited a case in which there was simulation of aplastic anemia, with enlarged spleen and without enlarged lymph nodes until six days prior to death. The bone marrow in this case was replaced by the characteristic tissue of Hodgkin's disease. Laur found the reticulocytes to be increased to from 5 to 13 per cent; he concluded that there is a spontaneous reaction in the marrow like that in pernicious anemia.

In summing up the data and forming a general impression, it may be stated that all cases show some degree of the cachectic type of secondary anemia; in scattered cases the anemia is of greater intensity, and in some instances it simulates either pernicious anemia or aplastic anemia, which is important in differential diagnosis.

*Platelets.*—Bunting held that the platelets are constantly increased in number and size; some of them are very large, being practically megalokaryocytic pseudopodia. He explained occasional low counts by the suggestion that there is an eventual necrosis of megalokaryocytes in the marrow, with resulting failure to form platelets. In one of his cases there were enormous pseudopodia-like masses (50 microns long) which he believed to be masses of megalokaryocytic protoplasm and their unconstricted pseudopodia, the remains of megalokaryocytes stripped of their protoplasm after passing through the lung from their point of origin in the bone marrow. McAlpin (using Ottenberg and Rosenthal's method of counting) found high platelet counts in 7 of 18 cases. Falconer did not find the counts high, although in general his results agreed with those of Bunting. Vasiliu and Goia, Cunningham and Burnam did not find an increase in a majority of cases; Miller and Boles found increased counts, as did Schreiner and Mattick.

In evaluating platelet counts a number of factors must be considered. Several papers have an indirect bearing on this. Bannerman, following the work of Bull, Delrez and Govaerts, and Cramer, Drew and Mottram, had reason to believe that platelets are concerned in resistance to bacterial infection. He was able to show that there is a general relationship between the body temperature (as in pyrexia) and the number of platelets in the blood; the two are parallel. He also indicated that the amount of exercise taken and the time of day when the

determination is made may affect the count. Bedson's work on the rôle of the reticulo-endothelial system in the regulation of blood plates showed that reticulo-endothelial blockade by particles of carbon is associated with a considerable increase in the number of circulating platelets. Koster noted the same association; he observed also that following the increase in platelets there is a sharp recoil, followed by a gradual diminution, even though the blockade is maintained. Bunting's idea concerning the platelet count may thus be justified. It seems hardly necessary to allude to the belief of many that the reticulo-endothelial system is deeply concerned in lymphogranuloma, and the speculation is interesting that perhaps these same factors are operative to some extent in this disease.

*Lymphocytes.*—Ziegler's statement that the lymphocytes are usually relatively and absolutely decreased has the support of numerous observers and is in keeping with the polynucleosis frequently encountered. Fabian stated that the lymphocyte count may be low—from 0 to 3 per cent—and that lymphopenia most frequently accompanies an absolute increase in the number of leukocytes, may occur at times in association with reduced leukocyte count, and is seldom noted when there is a normal leukocyte count. He also found at times a moderate relative lymphocytosis of transitory nature. Bunting gave a reduced percentage, with more marked reduction in the later stages. Muller and Boles found generally an early lymphocytosis with later lymphopenia. Terplan and Mittelbach stated that moderate leukocytosis with lymphopenia is the rule. Vasiliu and Goia found that 5 per cent of cases show lymphocytosis. Hayden and Apfelbach, Cunningham, Borsutzky and others stated that a majority of cases show lymphopenia. Straube divided his cases according to the relationship between the number of lymphocytes and the total white cell count. In the early forms there is lymphopenia with a normal leukocyte count; when complications are present, lymphopenia with leukocytosis, and in generalized and abdominal forms, lymphopenia with leukopenia. Hayden and Apfelbach's conclusions regarding the lymphocyte count in cases involving the gastro-intestinal tract are in agreement with Straube's third conclusion, that in abdominal (gastro-intestinal) forms there is lymphopenia with leukopenia.

Some cases show lymphocytosis, which is rarely pronounced. Fabian believed that lymphocytosis is usually moderate and transitory. Jaffé reported a case of lymphogranuloma of the intestine with extreme lymphocytosis (1,000 white blood cells, with 89 per cent lymphocytes). Gutig's case (cited by Ziegler) showed a rise in the proportion of lymphocytes of from 22 to 99 per cent just prior to death. The total leukocyte count was 2,000. Rolleston felt that usually there is leuko-

penia with relative lymphocytosis, especially when the spleen is involved. Weber agreed with him. Simmons and Benet stated that the lymphocytes are usually somewhat increased; they mentioned the effects of radium in producing a reduction in lymphocytes. Fox stated that the proportion of lymphocytes is usually normal. The effects of radiation on the lymphocytes must not be forgotten; this is given consideration under another heading.

*Transitional Cells.*—As Bunting has placed so much emphasis on the transitional leukocyte, his description is given: The nucleus stains sharply with Wright's stain; it is massive and of several shapes—knobbed, lobed, twisted, folded or ring-shaped. It may be so complex that it suggests a foreign cell. The protoplasm is clear blue, crowded with azure granules finer than those in a polymorphonuclear and of the same tint as those in platelets.

The normal percentage as given by different authors varies considerably: Bunting gave from 2 to 8; Wood, 2 to 4; Webster, 3 to 5; Gulland and Goodall, 3 to 10, and Naegeli, 6 to 8. McAlpin stated that, to be considered high, the count must be at least 5 per cent, which is a fair estimate.

Bunting's findings are that in Hodgkin's disease with a normal leukocyte count the transitional cells average about 10 per cent; with leukocytosis they average 6.4 per cent (a reduction) and with leukopenia they average 17.8 per cent (an increase). This indicates that there is a relatively large number of transitionals in the circulation throughout the disease. McAlpin's figures did not corroborate this; only 8 of 18 cases showed an increase in transitional cells. Burnam's large series of cases showed no increase in a majority of cases. Cunningham found the proportion variable, but in general increased. Schreiner and Mattick did not find an increase in transitional cells commonly, and Miller's figures were also low. Symmer's cases showed a uniformly low count. Muller and Boles stressed an increase in transitional cells.

Briefly summed up, the percentage of transitional leukocytes is variable. It is suggested that Bunting's description be used in future work in order that more uniform and dependable results may be obtained, for the constitution of a transitional cell is variously interpreted and it may be that the variable results can be traced to that source to some extent. If reliable figures bearing on Bunting's theory are to be obtained, certainly more expert identification is necessary than can be made by the average intern, whose results on such critical points are so frequently taken by authors in working up their cases.

Cunningham found 13.3 per cent transitional cells in a case of primary large round cell sarcoma of the mediastinum. He called attention to the probability of mistakes if Bunting's ideas are to be relied on.

*Megalokaryocytes.*—Bunting and others have seen these cells in the blood. Minot reported immature forms as present. They are undoubtedly rare.

*Mast Cells.*—Fabian, Rulison and Symmers (case 12, 5 per cent) have noted mast cells in rare instances.

*Polymorphonuclear Neutrophils.*—Fabian's statement that the most frequent change in lymphogranuloma is an absolute polymorphonuclear neutrophilic leukocytosis is concurred in by many observers, among whom may be listed Dimmel, Cunningham, Rauke, Muller and Boles, Bunting, Piney, Schreiner and Mattick, Burnam, Ziegler, Desjardins and Ford, Terplan and Mittelbach, and Falconer. Falconer agreed with Bunting that this is apt to occur after the first year of the disease. Simmons and Benet noted that three fourths of his cases showed an increase. From an estimate based on the compiled cases as well as on personal observation I believe that the great majority of elevated percentages fall between 68 and 85 per cent. The percentage may also, though uncommonly, be very low; Jaffé's case showed a total white blood cell count of 1,000, with 89 per cent lymphocytes. The increase in polymorphonuclear neutrophils has so frequently been noted that the conclusion may be justified that it commonly occurs, not in all cases, but in the majority.

*Eosinophils.*—An occasional case shows a very high proportion of eosinophils, a finding by no means constant, the higher percentages being rare. Baldridge and Awe found 83 per cent eosinophils in a case in which the total leukocyte count was 43,800. Rolleston cited 2 counts of 26 per cent and 69 per cent; Gysi found 67.5 per cent (white blood cells, 32,000). The usual percentage of eosinophils is much lower, being from 4 to 6 per cent in about 25 per cent of all cases, and normal in the others (Fabian). As regards the value of the eosinophil count in diagnosis, MacNalty, Dreschfeld and Barron held that the presence of eosinophils in association with enlarged lymph nodes helps materially in establishing the diagnosis. Terplan and Mittelbach believed that eosinophils play no rôle. Bunting stated that the percentage is low in the active stages and normal or slightly higher in the reactive or quiescent stages, and that it may form an index to the activity of the disease.

A possible association between eosinophilia and pruritus has been discussed by several authors. Favre insisted on a constant relationship between the two. Rolleston, however, cited 2 cases to controvert this: In the first there were 26 per cent eosinophils without pruritus, and in the second (E. Bellingham Smith's case), 69 per cent eosinophils without pruritus, although the patient in the latter case had some itching

earlier in the course, the count at the time being 39 per cent. Such observations occur in the examination of any large series of cases.

Klauder, Weber and Bode, and Stewart believed eosinophilia to be an expression of the allergic state. Barron expressed his belief in the possibility that Hodgkin's disease is of animal parasitic origin, such diseases being generally accompanied by eosinophilia. Montgomery suggested that involvement of the bone or bone marrow is to be looked for in the presence of eosinophilia; Weber and Bode, that the intestines are involved. Stewart, after careful study of a case of familial eosinophilic diathesis plus Hodgkin's disease, stated that "eosinophilia in the majority of cases is a specific reaction of the bone marrow in Hodgkin's disease." He also cited the literature on cases of Hodgkin's disease with hyper-eosinophilia. In concluding, he stated that the exaggerated eosinophilia in his case was apparently due to a well established familial allergic background (asthma and eczema), to a familial eosinophilic diathesis, to a personal allergic background (asthma in childhood), to the specific eosinophil-stimulating effect of Hodgkin's disease and to the added effects of arsenic therapy. Holzknecht cited 2 cases presenting eosinophilia. Page, Turner and Wilson brought the broader aspects of the problem to attention in an examination of 5,500 general medical cases, in 300 of which eosinophilia was present. The eosinophilia was associated with parasitic infections in 10 per cent of the cases, with rheumatic fever in 13 per cent, with chronic pulmonary disease in 13 per cent and with chronic nephritis and arteriosclerosis in 10 per cent; in fully 40 per cent, it occurred in isolated cases of various conditions and had no diagnostic significance.

The work of Meulengracht and Holm must also be given consideration, particularly because liver has been rather widely used in the treatment of all types of anemia by physicians in general. They stated that eosinophilia sometimes appears suddenly in the course of treatment of pernicious anemia with liver and persists as long as the administration of raw liver is kept up. Fried liver rarely produces this phenomenon. As controls they used patients with other diseases, and the same result was obtained. Such percentages of eosinophils as 20, 40 and even 74 were found.

Griffin and later Harrison reported the occurrence of eosinophilia in association with splenomegaly, and involvement of the bone marrow and lymph nodes. Ringoen discussed the origin of eosinophils. Hajos considered the relationship of these cells to the formation of immune bodies. Schwarz reviewed 2,758 articles on eosinophilia.

*Basophils.*—Cunningham's 10 cases showed basophil counts of from 0 to 1.5 per cent. Bunting's figures were similar. Basophils are not affected by the disease.

*Large Mononuclears.*—Cunningham's figures show a variation of from 1.5 to 22.3 per cent (normal, from 4 to 8 per cent); in 7 of 10 cases the percentage was well above the normal, and in only 2, below. Borsutzky noted a decrease in two thirds of his cases in children. Falconer found a fairly constant increase. Bunting found no change in numbers. Straube noted an increase but believed it to be of small importance. Brandt noted an increase only in isolated cases. Piney accepted the contention of Aschoff and Kiyono that the monocytes are derived from the reticulo-endothelial system but qualified his belief by stating that the monocyte is as much a myeloid cell (from the myeloblast) as is any other granular leukocyte.

*Myelocytes.*—Aubertin found myelocytes occasionally, usually in cases showing marked polynucleosis. Fabian found them at times, with higher percentages exceptional.

### RETICULO-ENDOTHELIUM

The reticulo-endothelial system has been brought into considerable prominence, chiefly by Piney, who repeatedly suggested "that Hodgkin's disease is to be regarded as being essentially a proliferation of reticulo-endothelium and its derivatives," and called it a reticulo-endotheliosis. Rolleston, in commenting on Piney's theory, brought out an interesting point—that if the process were primarily a proliferation of endothelial and reticular cells, "Kupffer's cells in the spleen and liver should be constantly and predominantly affected, and this is not the case."

Of practical interest, especially in diagnosis, are a number of papers, most of which are by German writers, on various phases of "reticulosis." In some of the cases described the condition bears such a marked resemblance to true Hodgkin's disease that absolute distinction may be impossible. I had a case in which the condition was diagnosed as Hodgkin's disease by competent pathologists and had many of the characteristics of that disease. The histologic picture, however, could not be considered as quite typical; there was extensive proliferation of large pale cells in the nodes, almost exactly like those in the case of Schultz, Wermbter and Puhl, which showed hyperplasia of the reticulo-endothelial cells together with the formation in several organs of nodules made up of large phagocytic cells. The case of Tschistowitsch and Bykowa was similar; the diagnosis was reticulosis universalis aleukemica. These authors recognized that lymphogranuloma in some ways parallels those little known states. Certainly, the differences between a reticulo-endothelial hyperplasia, such as their case presented, and the hyperplastic or active cellular stage of lymphogranuloma are no greater than those separating lymphogranuloma in the earlier stages and a small cell lymphosarcoma.

Tschistowitsch and Bykowa included a good bibliography on the general subject of reticulo-endothelium. Vehlinger, in addition to reporting a case of aleukemic reticulosis, offered a classification of reticulo-endothelial hyperplasia. Jaffé thoroughly reviewed the literature on the reticulo-endothelial system. Watson's review covered the American literature for 1926. Ferrata's work on the blood includes a full discussion of reticulo-endothelium. Further material on reticulo-endothelium and lymphogranuloma may be found in the section devoted to histology.

### PORTALS OF ENTRY

Numerous attempts have been made to locate possible points for the entrance of an etiologic agent. The most frequently mentioned portal is the tonsil; an invasion at this point is followed by cervical lymphadenopathy. Cases have followed tonsillectomy (Burnam [5 cases]; R. Paltauf; Simmons and Benet; L'Esperance), other cases have followed acute or chronic lesions around the mouth, throat or ear (MacNalty, otitis media; Taylor, tonsillary abscess; Arkin, chronic tonsillitis; Cunningham, tonsillitis and diphtheria). Carious teeth were mentioned by Desjardins and Ford, who were impressed by the frequency of the relationship between the adenopathy and chronic lesions of the mouth, throat, teeth, tonsils and nasopharynx.

Feer expressed the theory that if the portal of entry were by way of the pharyngonasal cavity, the cervical nodes would be involved; if through the lungs, the mediastinal nodes, and if through the intestinal mucosa, the mesenteric and retroperitoneal nodes. If entry is by way of the intestine, the process spreads through the thoracic duct, particularly to the supraclavicular nodes of the left side, an observation of clinical value. Kraus traced a possible portal to the upper lobe of the right lung by estimating the relative age of the lesions, considering that the ones apparently the oldest were the first to appear. The danger of drawing such a conclusion is evident, because of wide variations in the structure of nodes of the same or apparently the same age. Saupe held that pulmonary foci are not so rare as is commonly maintained. Cunningham observed a case of intestinal origin.

Symmers stated that primary enlargement of abdominal or of abdominal and thoracic nodes combined is 10 times more common than primary enlargement of the cervical nodes. Ewing supported this view, adding that the superficial nodes which first attract attention are merely the outlying portions of an internal lesion. This marks a definite advance in the modern concept of the disease.

Cases following various infections are not rare. Corbeille found that in more than one third of cases in children there was a history of infectious disease at the onset of the typical symptoms. Bunting's case

of involvement of the inguinal lymph nodes followed cystitis. I have seen 2 cases following pulmonary disease (pertussis, influenza). The possible rôle of trauma is considered under the heading of medico-legal aspects.

### INVOLVEMENT OF VARIOUS ORGANS

*Lungs.*—Pulmonary involvement is common, depending to a certain extent on the preponderating distribution of the diseased nodes, i. e., mediastinal or abdominal. Baldridge and Awe reported 14 cases, of which 7 (50 per cent) showed involvement of the lungs. It is probably possible to recognize three types of pulmonary involvement: massive invasion of the hilus by mediastinal enlargements, extensions into the lung proper by radiating bands following the interlobular lymphatics (Simonds), or small isolated nodules scattered throughout. The lung may be replaced by the new tissue, according to Schottelius and Chiari.

H. Weber, in discussing 7 cases of marked pulmonary involvement, called attention to Wohlwill's classification of pulmonary types of Hodgkin's disease: 1. Involvement begins in a bronchus and spreads along the bronchial tree, surrounding it and simulating bronchogenic carcinoma. 2. Multiple nodules of varying size are scattered throughout the lung, grossly resembling metastatic tumor of the lung. 3. The lung is invaded by continuity of a process in the hilar lymph nodes. Lignac described lesions investing the bronchi and vessels in a mantle-like fashion, similar to Wohlwill's type 1.

Other phases are: filling of the alveoli with granulomatous material (MacCallum); tracheo-esophageal fistula (H. Weber); erosion of the trachea and bronchi (MacCallum; Ness and Teacher; Fraenkel and Much; Meyer; Steiger); stenosis of the bronchi (Weber; Ziegler; Ferrari and Comotti); cavitation (Dvorak; Shapiro), and pressure atrophy of the wall of the chest (Lyon). Wessler and Greene noted that enlargement of the right paratracheal nodes occurs frequently in Hodgkin's disease, but uncommonly in other diseases. Terplan's case showed marked involvement on the right side, with an isolated nodule in the apex of the right lung, which he considered to be a primary focus. Bouslog and Wasson described formation of cavities simulating those in tuberculosis, death being due to pulmonary hemorrhage. Cooper's case was unusual, as the patient was 72 years old and showed an acute mediastinal process without noticeable enlargement of the superficial lymph nodes. Other reports of general interest are those of Kuckuck, Albot and his co-workers, and Lignac.

The pleura is occasionally involved (Reckzch; Yates and Bunting; Hecker and Fisher; Symmers; Lyon), with effusion in some instances (Ziegler; Waetzold; MacCallum; Fabian; McAlpin and von Glahn; Edsall; Weber and Ledingham; Graeka).

The larynx may be involved, according to Chatellier and Halphen.

*Liver.*—Limitation of the process to the liver is unknown (Rolleston; Muller and Boles), but the liver is generally, though not always, involved in conjunction with the spleen. The following percentages of incidence of involvement of the liver are taken from the literature: Barron, 50; Ziegler, 60; Rolleston, 50; Symmers, 71; Terplan and Mittelbach, 50; Cunningham, 17. On the basis of these figures, the average percentage of cases in which involvement of the liver occurs is about 50. Burnam, speaking of clinically enlarged liver, gave an incidence of but 4 in 173 cases; MacNalty, 1 in 5, and Barron, over 50 per cent. Hayden and Apfelbach stated that the liver and spleen are usually not enlarged in lymphogranulomatosis of the gastro-intestinal tract. Barron remarked that "it is likely that the peribiliary infiltration produces jaundice more frequently than does pressure of enlarged lymph nodes or tumor masses against the large bile ducts." According to Coronini, icterus in lymphogranuloma is obstructive, as a result of: (1) compression of the common duct alone; (2) obliteration of the common duct alone; (3) changes in both the extrahepatic and the intrahepatic ducts; (4) changes limited to the intrahepatic ducts. Obstruction of the extrahepatic bile ducts may be due to pressure by enlarged nodes or to invasion of the duct wall by lymphogranulomatous tissue. Within the liver the interlobular ducts may be compressed by involvement of the interlobular stroma. Symmers found that in his series "the nodular foci arose in the periportal spaces and were initiated by hyperplasia of the lymphoid cells in the walls of the portal veins, followed by the appearance among the lymphocytes of mononuclear and multinuclear giant cells with or without the presence of eosinophiles and eosinophilic myelocytes, the whole supported in a connective tissue reticulum, the nodules expanding in such fashion as to subject the neighboring lobules to atrophy from pressure, but never directly infiltrating them." In one of his cases he found changes essentially composed of great thickening of the intrahepatic portal veins, in the walls of which was the typical lymphogranulomatous process, the connective tissue replacing the organ; he believed that these changes constituted a hitherto undescribed phase of the pathologic process.

Terplan and Mittelbach cited an unusual case involving the liver and spleen (case 22), in which the liver weighed 3,300 Gm. Barron described a case in which the liver weighed 3,000 Gm. Crouzon, Bertrand and Lemaire noted a case with amyloid changes. The simultaneous occurrence of tuberculosis and lymphogranuloma in the form of well defined discrete and separate nodules in the liver has been described several times.

*Spleen.*—The primary splenic form of Hodgkin's disease is rare, even if such a state is admitted to exist. Opinion is divided on this

point. Ziegler allowed the inclusion of this form. Symmers, L'Esperance, Wade, Mellon, Doncaster, Muller and Boles, and Burnam cited cases suggestive of such a condition; yet in none of these cases can the diagnosis be considered as proved. In Muller and Boles' case autopsy showed involvement of the spleen and bone marrow, without enlargement of the lymph nodes. In the other cases the diagnosis was based on clinical and surgical findings. Larrabee's case, in which splenectomy was done because of an enlarged spleen, can hardly be accepted, as the lymph nodes in the neck were palpable before operation. The patient recovered and was well two years afterward. The greatest handicap in deciding the issue is the lack of adequate autopsies in the cases reported and also the difficulty, if not impossibility, of the determination of the relative age of the individual lesions. The criterion of fibrosis does not hold. The question should remain open.

The majority of writers agree that splenic lesions are common. Barron stated that they are usually miliary or submiliary, with occasional larger masses. The involvement is often observable on microscopic examination, at times being definitely specific and at times only suggestive. Ziegler's estimate that from 65 to 75 per cent of cases show splenomegaly is well borne out by the following compilation of data from the literature: Of 321 cases, 226 or 70 per cent showed some degree of splenomegaly (Murray; Turnbull; Symmers; Muller and Boles; MacNalty; Barron; Cunningham; Terplan and Mittelbach; Clark; Simmons and Benet). The greatest weight noted was that in case 22 of Terplan and Mittelbach, 3,720 Gm. Spleens of normal size or smaller than normal are fairly common.

The spleen in limited gastro-intestinal Hodgkin's disease is not involved as often as one might suppose. Hayden and Apfelbach stated that the spleen and liver are usually not involved, which supports Partsch's statement. In cases in which the gastro-intestinal tract is involved as a part of an abdominal distribution, the spleen is commonly enlarged.

MacNalty made an interesting observation—that the splenic enlargement is more marked in the period of pyrexia, and that the organ may be palpable only at this period. Tenderness or pain in the flank may be due to infarction.

Corbeille, after observing 33 cases in children, stated that splenic enlargement is the most frequent abdominal sign of the disease in children. Holler and Paschkis reported an unusual case in which the clinical diagnosis was hemolytic jaundice and splenectomy was performed. The diagnosis of Hodgkin's disease was unexpected.

*Suprarenal Glands.*—Involvement of the suprarenal glands is rare. Ziegler had seen no authentic cases. Simmons examined the cases of Yamasaki, Fraenkel and Much, and Paunz. Paunz gave an excellent

description of numerous focal lesions in the suprarenals. Barron mentioned a case but did not go into detail. Bine described a case with extensive destruction of the suprarenals by necrosis, little normal tissue remaining, and without special clinical symptoms.

Enlarged nodes surrounding the suprarenals, practically embedding them in a mass of lymphogranulomatous tissue, are described more frequently. Nieśjkowski, Fowler, Bramwell, Symmers and Laporte reported on this aspect. Rolleston believed that the symptoms produced depend on irritation of the sympathetic nervous system rather than on actual involvement of the suprarenals. Symmer's case of acanthosis nigricans, in which there was lymphogranulomatous invasion of the celiac plexus without involvement of the suprarenals, supports this view.

*Gastro-Intestinal Tract.*—Hayden and Apfelbach, in 1927, covered the subject of gastro-intestinal Hodgkin's disease thoroughly, reviewing 26 cases and presenting 3 new ones. They made a special attempt to form a group of diagnostic features suggestive of lymphogranuloma of the gastro-intestinal tract—fever, diarrhea, abdominal pain, rapid cachexia, secondary anemia and leukopenia or a normal white blood cell count. The cases fell into three clinical groups resembling other more common entities—ulcerative enteritis and colitis, particularly the tuberculous forms, gastric carcinoma and intestinal obstruction. They noted that the liver and spleen are usually not enlarged and that nodules in these organs are uncommon. In a few cases the superficial nodes were enlarged, but this was unlike the more common extensive enlargement of generalized Hodgkin's disease. Vasiliu and Goia found the chief clinical symptom to be "dyspepsia," which is worse at night. The patients are supposed to have a gastropathic condition, as the lymph nodes are too small to be noticed on examination. Coronini paid particular attention to the pathology of lymphogranuloma of the gastro-intestinal tract. The lesions may involve this tract exclusively, chiefly or as a part of a generalized process. The lesions may appear as nodules arising in the submucosa which protrude into the lumen and often ulcerate, as smaller nodules scattered throughout the wall or as broad areas of granulomatous tissue which invades the wall widely and diffusely.

There are a number of articles on the surgical aspects of lymphogranuloma of the gastro-intestinal tract, mostly involving the reaction of localized foci (Steindl; Ringdal; Ogloblina; Sussig). Sussig reported 3 cases, and stated that the disease rarely occurs in this tract.

Primary isolated lymphogranuloma of the gastro-intestinal tract is rare, but evidently occurs. The case of Goedel seems to prove this. The condition was diagnosed clinically as appendicitis, and the patient was operated on; part of the ileum, cecum and mesentery were removed, and on microscopic examination showed lymphogranuloma. The patient

died of peritonitis after four days, and autopsy showed no evidence of lymphogranuloma in any other organ than the ileocecal valve. Howell described a case involving the retroperitoneal glands in which the course closely simulated that of acute appendicitis and the patient was operated on. Singer cited the first case of primary isolated lymphogranuloma of the stomach reported in this country. Autopsy showed no other involvement. DeJong's case involved a loop of small intestine, but he did not include a report of the autopsy. Drope's case involved the stomach, with limitation to the gastro-intestinal tract and mesentery. Minot and Isaacs, reporting a series of 477 cases, chiefly of abdominal Hodgkin's disease and lymphoblastoma, stated that "Hodgkin's disease rarely causes large or multiple primary lesions of the gastro-intestinal tract while lymphosarcoma and pseudoleukemia often do so." Ikeda considered Hodgkin's disease of the gastro-intestinal tract in an article on lymphatic leukemia and included references to the literature. Wahl, Chand, Grevillius and Delanne and Lepage reported cases. Lang believed that lymphogranuloma of the gastro-intestinal tract probably started in the connective tissue of the mucosa and submucosa. References to the German literature were given. Wells and Maver, in 1904, collected the first cases of pseudoleukemia gastro-intestinalis. Lignac found a lymphogranulomatous ulcer of the lower end of the esophagus, without the symptom of dysphagia during the life of the patient.

*Bone.*—Opinion as to involvement of the bones varies widely. The reason may well be ascribed to the unequal determinative values conveyed by gross and microscopic examination of tissues and the inadequate diagnostic data furnished by roentgenograms. Reports based on roentgenographic findings are numerous, but to make a statistical study of the frequency of involvement of the bones on the basis of these reports alone would lead to considerable error. Tetzner found lesions of the bones in 9 of 10 cases in which autopsy was performed, and furthermore showed that certain vertebral lesions found at autopsy could not be demonstrated by roentgen examination, even when sagittal sections of the bones were made. Structural changes in the bones are of course demonstrated by roentgen examination, but the osseous lesions of lymphogranuloma are frequently not accompanied by such gross alterations. Symmers stated his belief that the marrow is always involved, but only thorough gross and microscopic examinations of the bones in numerous cases can decide that important point.

Ziegler believed that bone was involved in many cases, some of which showed very early osseous lesions. Blount's case illustrates such early involvement, the lesions of the bones preceding the lymphadenopathy by two years. Hamar's findings were similar.

Primary involvement of bone was reported by Montgomery. He stated that in such cases the disease may closely simulate bone tumor

or osteomyelitis and that the diagnosis rests finally on roentgen examination of the entire skeleton, with biopsies of bone to settle the question. Krumbhaar's unusual case was limited to the spleen and the bone marrow, the histologic picture of the marrow of the femur suggesting that the disease was primary in that site.

Arnell held that marked eosinophilia in lymph nodes points to an essential irritation and involvement of the marrow and that careful examination of the skeleton should be made. Stewart's observation that eosinophilia (in the blood) in a majority of cases may be considered as a specific reaction of the marrow in lymphogranuloma may be used in support of Arnell's contention. There has been frequent mention of Symmers' belief that the marrow is always concerned in this disease, and that the eosinophils in the affected nodes are derived from the blood, originating in the bone marrow.

Cases of general interest may be found in the papers of Saupe; Belot, Nahan and Kimpel; Baldridge and Awe, and Dresser and Kremser. Tetzner reviewed the literature and reported 10 new cases (with autopsies) in considerable detail, particularly with regard to involvement of the spine. Askanazy considered osseous lesions from the pathologic point of view.

Osteosclerosis (osteitis ossificans, endosteitis ossificans, condensing osteitis) in relation to Hodgkin's disease was discussed by Zypkin. He considered that the polymorphic stage of Hodgkin's disease is represented by an embryonal connective tissue from which bone can be formed, and he mentioned also the possibility of such formation of bone by an indirect route—through the commonly seen fibrotic stage which later becomes bone. He noted particularly the cases of Schwartz, Assmann, Baumgarten and Hammer. Osteosclerosis is much more frequent, although by no means common, in leukemias (Goodall; Weber; Sternberg; Fabian; Baumgarten; Zypkin; Kaufmann). Hulten recently cited a case of complete sclerosis of the second lumbar vertebra in lymphogranulomatosis.

Widespread lesions of bone were reported by Lockwood, Johnson and Narr. Matziani in a similar report stated his belief that such lesions are due to direct localization and not to extension from adjacent organs. Lesions produced by extension have been described in numerous instances and possibly form the larger part of the gross disease picture in bone. Involvement of the sternum, ribs or thoracic vertebrae is perhaps most frequent. Lortat-Jacob believed that the richness of the osseous marrow in the sternum is a reason for this localization. Düring and Cone cited such cases. While true infiltration of the spinal marrow is not frequently seen (Vasiliu and Goia; Robin), erosion and extension are common. One must not fail to appreciate how seldom the skeleton is examined microscopically, which may account for much

of the apparent rarity of infiltrative or metastatic lesions. Fraenkel's finding of granulomatous nodes, identical with those found in the spleen, in the general bone marrow should stimulate more careful search for such lesions. Sherman noted that metastases to bone react differently to x-rays than do lymph nodes, and particular caution was advised in the irradiation of vertebral lesions because of the possibility of producing local reactions in them, with consequent paraplegia.

Rolleston reported a rare finding—synovitis. The arthritis was usually transient and not well marked. Pfahler described involvement of the sacro-iliac joint.

In summing up the data on the lesions of the bones in Hodgkin's disease, the following points are stressed: (1) more careful and extensive roentgen examination of the entire skeleton, (2) biopsies on osseous lesions, (3) complete microscopic examination of numerous bones at autopsy whether they are grossly involved or not and (4) more careful description of the type of osseous lesion, and notation as to whether it is definitely traced to erosion, extension or metastasis.

*Skin.*—Involvement of the skin is present in a certain number of cases. It may be manifested merely by pruritus or by actual and more or less specific lesions. Ziegler's review showed the skin to be involved in 25 per cent of 70 cases of Hodgkin's disease. More recent figures are those of Cole (39 per cent of 33 cases) and of Barron (16 per cent of 24 cases). This is therefore a fairly common phase of the disease.

Pruritus may exist alone or with morphologic cutaneous lesions. Burnam reported it as present in 31.8 per cent of the series of 173 cases, and as being an initial symptom in 12 cases. He encountered it without definite lesions of the skin in 34 cases (19 per cent). Cole found it present in 8 of 33 cases (24 per cent). Barron, in a study of 24 cases, found the skin involved in 4; all of these showed pruritus at some time, and this symptom preceded the development of the lesions by several years. Ziegler's observations were similar. Desjardins and Ford reported pruritus as occurring much less frequently (in 9 per cent of 135 cases). Weber and Bode believed it to occur usually early in the course and seldom late. Favre and Colrat went so far as to designate the disease "adénite prurigène éosinophile" as a mark of their belief in the close association of pruritus and eosinophilia. Mariani corroborated this, but Cole refuted it, finding that the attacks of pruritus generally accompany a glandular flare-up. The cause of the pruritus is unknown, but various theories are offered. Paltauf held it to be caused by substances derived from the altered lymph nodes, and in this Shelmire and also Desjardins and Ford agreed with him. Other authors have referred the pruritus to a disturbance of the nervous system, such as irritation of the sympathetic system (Golay). Milian and Blum felt

that the pruritus may be due to radiculitis and be analogous to the pruritus of tabes dorsalis.

Ulceration is not common. Traut recorded the first case of spontaneous fistula over a mass of lymphogranulomatous tissue. Cole and also Langley reported cases of ulceration. Bine's patient showed an ulcer of the palate and a slough of a hemorrhoid without enlargement of the lymph nodes.

Primary Hodgkin's disease of the skin is described by a number of authors (Haxthausen; Kren; Saalfeld; Reisenberg and Kradlicky; Nanta and Chatellier).

Herpes is occasionally seen. Pancoast and Pendergrass reviewed the theories as to its causation—nerve irritation, pressure on a nerve by tumor tissue and toxic products producing a parenchymatous neuritis. They cited 4 cases. Mariani regarded all classic herpes as due to injury to the nervous system. Certainly it would seem that pressure on a nerve or on its spinal ganglion and also toxic products derived from the diseased tissue could cause this lesion. Lockwood, Johnson and Narr reported a case in which herpes zoster was the first symptom, and which later showed extensive destruction of the lumbar vertebrae.

Pigmentation occurs more rarely. Desjardins and Ford reported 2 cases. Laporte, Nieszkowski, Fowler, Bramwell and Symmers reported cases of pigmentation in association with masses of lymphogranulomatous tissue about the suprarenal glands. Rolleston believed pigmentation to be due to irritation of the sympathetic nervous system rather than to involvement of the suprarenals. Symmers reported a case of acanthosis nigricans with invasion of the celiac plexus and without involvement of the suprarenals.

The name "chancre lymphogranulomateux" was used by Nanta and Chatellier to designate an initial nodule which some believe places the disease in the same group as syphilis, tuberculosis and sporotrichosis. The similarity of this form to mycosis *d'emblée* is marked. Sharlit reported a case in which the surface lesions were limited to the oral and genital mucosa.

It is generally agreed that lymphogranuloma may occur in the skin in two forms—either with the specific histologic structure, which was first described by Grosz, or without this specific structure. In the latter form it may manifest itself by pruritus, pigmentation, edema, a prurigo-like exanthem, petechiae, bullae or urticarial lesions. Wise, and Jones and Alden described cases of generalized lymphogranulomatosis of the skin. Howard Fox and Cole reviewed the general aspects, as has Shelmire more recently. Miller, MacCormac, Arzt, McCarthy, Rulison and Keim have contributed articles of general dermatologic interest. McCarthy included the histologic aspects in his recent work on the histologic changes in the skin.

*Genitalia (Female).*—Gemmell described 17 cases in females in which it was possible to obtain a menstrual history. In 14 there was oligomenorrhea, in 3 menstruation was normal, and in 10 the patient was pregnant. In 25 of 57 cases the disease began during periods of amenorrhea. He considered the possibility of ovarian hypofunction. Winkelbauer and Priesel's case of possible placental or hereditary transmission is remarkable; the disease was present in both the mother and a newly born child. Minot and Isaacs noted the frequency of menstrual disorders but did not feel that the occurrence of such disorders in association with lymphoblastoma must be attributed to disease within the abdomen. Barron described a completely normal pregnancy occurring six years after the development of enlarged nodes.

Involvement of the uterus is rare; to my knowledge but 2 cases have been reported (Jessup; Lewinski). Ovarian involvement was described by Wallthard and by Mousson. Szenes' case presented involvement of the internal genitalia and bladder, a condition which was unusually refractory to treatment.

*Nervous System.*—The first to describe involvement of the nervous system was the pioneer Murchison, in 1869, who also first described the type of fever frequently associated with Hodgkin's disease. Since his time, a limited number of reports have appeared dealing with lymphogranuloma of the nervous system, most of them from clinical sources. Such involvement has generally been considered rare, or at least uncommon. Ginsburg, in an analysis of 35 consecutive cases, was able to find definite evidence of involvement of the nervous system in 10 (27.7 per cent), which shows it to be a rather common phase of the disease. In the majority of cases the visceral lesions overshadow those of the nervous system, but occasionally the reverse may obtain (Ginsburg; Paullin).

The underlying pathologic process has usually been a tumor-like growth with compression of any compressible tissue within reach. It is to this phenomenon that most, but not all, of the paraplegias in lymphogranulomatosis are traced, the spinal cord, and rarely the brain, being so situated that any encroachment on the limited confines of the vertebral canal or cranium is certain to produce pressure on the cord or brain. Filling in of, or extension through, the intervertebral foramina, periosteal thickenings, erosions of vertebral bodies and infiltrations of the spinal meninges, either arising in situ or penetrating from an extravertebral initial source, are the most commonly found lesions (Paullin). The effects are almost always rather slow and progressive, but may be acute, even resulting in sudden death, as in MacCallum's case, in which there was erosion of the odontoid process with spontaneous fracture. Paullin's case of sudden death, with marked cerebral crisis, is unique, as no morphologic cause could be found. The effects may also be transi-

tory, as seen by the clearing up of a transverse myelitis in Simmons and Benet's case and in Forrest's case. Roentgen treatment will produce alleviation of such manifestations and must be considered (Blakeslee). Extremely rarely the point of attack may be the brain, as in Burnam's case. Fraenkel, East and Lightwood, Poynton and Harris, Paullin, Mueller, Blakeslee, Hale White, Weber, Belot, Simmons and Benet, and Rolleston have contributed case reports and discussions illustrating the mechanism and effects of pressure. So far, I have found but a single case of actual metastatic tumor in the parenchyma of either the brain or the cord (Power and Hala).

In some cases, however, the neurologic disturbances cannot be traced to the effects of compression. Allan and Blacklock cited a well defined case of Hodgkin's disease with autopsy in which the cerebral nervous system showed purulent meningitis (bacterial) of the brain and cord, with myelitis below the middorsal segments. Weber stated with regard to symptoms of involvement of the cord that "in by no means all the cases were these tumor-like growths affecting the vertebral column within the vertebral canal." He held that some of these lesions are found to be syringomyelia, pachymeningitis interna, tuberculosis associated with lymphogranuloma, or myelitis of the cord itself.

Forrest's case showed no lymphogranulomatous lesions of the vertebrae, canal or meninges, but there were slight degenerations of several tracts of the cord. He cited 4 other parallel cases. Shapiro contributed 2 cases, one of transverse degenerative myelomalacia and one of subacute posterolateral sclerosis. Burnam's series included a case with symptoms of meningitis. Johnston's case presented two separate neurologic processes—degeneration of spinal tracts due to anemia and intoxication and pressure atrophy due to perineural infiltration.

The cause of such lesions must, of course, vary in the different cases (Weber). Forrest offered as the theoretical explanation for the lesions in his case liberation of toxins, pressure by the pathologic tissue on vessels supplying the cord or general anemia; he felt that anemia was the most probable cause. One must not lose sight of the fact that aside from the possibility of pressure on blood vessels their walls may be invaded so as to produce local anemias. Shapiro's explanation for his case of myelomalacia is that it was produced by nonspecific proliferation of the arachnoid mesothelial cells in the "duraneural angle," which blocked the lymphatic drainage and led to lymph stasis. The possibility of this phenomenon is demonstrated by the excellent illustrations of Spielmeyer. Shapiro considered the formation of toxins as the cause of the lesions in his second case. Weber asked whether high voltage roentgen therapy could cause transverse degenerations of the cord leading to paraplegic effects. Rolleston considered the possibility of an arsenical neuritis being responsible for paraplegia in Carlill's case.

Reports of unusual neurologic manifestations are scattered throughout the literature. Baldridge and Awe cited a case in which Horner's syndrome was present, possibly due to paralysis of the cervical sympathetic system. MacNally mentioned the occurrence of irregularity of the pupils when the sympathetic nervous system was involved. Simmons and Benet listed 2 cases with exophthalmos. According to Paullin, nervous symptoms may precede all others.

The occurrence of herpes zoster is fairly common. Weber, in discussing Carslaw and Young's case, called attention to the possibility of the involvement of the posterior roots and ganglions by the abnormal tissue, stating that no cases of herpes zoster had been reported with such infiltrations, perhaps because the vertebral canal was not examined at autopsy. Pancoast and Pendergrass reviewed the theories as to the cause—irritation of a nerve, pressure on a nerve by tumor and toxic effects producing a parenchymatous neuritis. They stated that other malignant conditions also cause this lesion. Mariani regarded the various clinical forms of herpes as merely variations of a fundamental process of reaction, such as injury to the nervous system. He did not refer specifically to lymphogranuloma.

Pruritus as a neurologic symptom, according to Milian and Blum, is possibly due to radiculitis, being analogous to the pruritus of tabes dorsalis. Golay stated that it may be due to irritation of the sympathetic nervous system. Paltauf, Shelmire, and Desjardins and Ford interpreted pruritus as of toxic origin, usually caused by substances in the circulation derived from the diseased lymph nodes. The association of eosinophilia was greatly stressed by Favre and Colrat. Mariani also noted a close relationship. Cole, however, could not corroborate this, finding that the attacks of pruritus accompany a glandular flare-up.

Pain has generally been considered as absent in the enlarged nodes, but they may at times present this symptom. MacNalty vividly described such cases; the pain occurs chiefly during periods of pyrexia, the nodes being hot, swollen, soft and tender; as lysis occurs, the condition recedes and the nodes become painless until the next period of pyrexia occurs. Pain is most commonly found in abdominal cases, in which it may be vague, moderate or intense, and either generalized over the abdomen or so localized as to simulate closely several conditions (perforation of an intestinal ulcer as in typhoid [McAlpin and Von Glahn], acute appendicitis [Howell], peritonitis [Whillington] and chronic appendicitis or cholecystitis). In a case of mine the abdominal pain was excruciating and almost continuous, morphine being used freely. Laparotomy was performed, and two large retroperitoneal masses were found in the region of the celiac plexus. High voltage roentgen therapy gave considerable relief. Fox and Farley mentioned the occurrence of paroxysmal pain in the lower part of the abdomen in cases of granuloma of

the abdomen. Cunningham, in reporting a series of 25 cases, called attention to pain as a reason for consulting the physician (pain alone in 4 instances and tumor and pain in 2). Desjardins and Ford found pain frequently. They described the symptom as of two types: (1) pain due to pressure phenomena and (2) intermittent pain occurring in bones and joints and present in the later stages, moving from place to place, and examination showing nothing to account for it. Isaac mentioned backache as a symptom. Ducamp and Rimbaud described pain due to a mediastinal mass; it was relieved by irradiation.

Graber cited a case of lymphogranuloma with paroxysmal tachycardia in which fatty degeneration of the vagus nerves was found, due to pressure by a mediastinal mass. This is exceptional, as most cases of paroxysmal tachycardia have not been shown to be due to stimulation of the extrinsic cardiac nerves. MacNalty described cardiac irregularity resulting from pressure of enlarged cervical nodes upon the vagus.

Weil (1931) collected reports of 43 cases of involvement of the spinal cord from the literature, and added a report of 3 new cases, with operative findings and autopsy observations. The involvement of the cord was cervical in 16 per cent, thoracic in 80 per cent, and lumbosacral in 4 per cent.

## ETIOLOGY

The etiology of lymphogranulomatosis constitutes a most difficult phase of the subject, for it is closely linked with speculation and theory concerning the true nature of the disease. Stewart and Dobson grouped the different views under the following headings: (1) an atypical form of tuberculosis; (2) a specific infection by a diphtheroid bacillus; (3) a granuloma of unknown etiology; (4) a neoplastic disease. These several categories, while comprehensive, do not sufficiently bring out all of the possibilities. An attempt will therefore be made to summarize briefly the reported evidence.

As to lymphogranuloma being an atypical form of tuberculosis, the question will be discussed under a separate heading.

The second point of view, that lymphogranuloma is due to infection by a diphtheroid bacillus, is still maintained by some authors and contradicted by others. Bunting and Yates described lesions produced in monkeys by injection of the bacillus which they believed to be the etiologic agent, but with the exception of certain reactions resembling Hodgkin's disease the results did not establish the theory. Twort, in a long series of experiments, could not confirm it. The diphtheroid organisms have been held to be merely air-borne laboratory contaminants which are not found when strict sepsis is maintained in laboratory procedures.

The idea that lymphogranuloma is a granuloma of unknown etiology has the most adherents. Twort advanced a theory involving a filtrable virus on the basis of a study of allied diseases unquestionably caused by a virus, such as leukemia of fowls and pernicious anemia of horses. Favre and Croizat were of the opinion that the specific histologic picture suggested the local reaction to a virus which tended to display unequal activity in different nodes or tissues.

Barron advanced the opinion that lymphogranuloma might be due to an animal parasite and suggested that the inclusion bodies of Kuczynski and Hauck might be such parasites or the cellular reaction to them. He further stated that certain features of lymphogranuloma, such as the peculiar relapsing type of fever, the eosinophilia and the nontransmissibility to animals, militate against vegetable parasites as causative agents. Kofoid's theory, proposing an ameba, could not be confirmed by Schreiner and Mattick, or by Twort.

Several observers have reported the presence of fungus-like bodies. Kuczynski and Hauck believed that the etiologic agent is a type of higher bacteria midway between Bacillus tuberculosis and Actinomyces. They have described inclusion bodies in the cells of the lesions. Merk reported a thallophyte as the etiologic agent. Haythorn reported the finding of a monilia, which he believed to be a secondary invader. Twort, in his most recent and extensive report, stated that he could not find any evidence of fungi.

Busni's organism is described in the section on bacteriology; the claims are broad, and no corroboration has appeared. Grumbach's organism has been claimed to be etiologic.

Bunting and Yates suggested that staphylococci, which they found in almost all cases, play the part of secondary infectious agents, and that secondary infection plays a part in the development of the disease.

Piney stated his views as to lymphogranuloma being a reticuloendotheliosis, and Brandt agreed with him. "Lymphogranulomatous tissue is a mere mark of a severe injury of the reticuloendothelials through different causes and is not a disease of a specific sort." This idea is a distinct departure, and might be invoked to explain the occasional "atypical" cases of lymphogranuloma, so confusing to the microscopist.

The theory that lymphogranuloma is a true neoplasm has been advanced, especially in the more recent publications. Perhaps the oldest concept of neoplastic origin is that involving the lymphoblast (Mallory, Warthin, and others), which assigns Hodgkin's disease a place in the category of lymphoblastomas under the designation "lymphoblastoma of the Hodgkin's type," or that of "scirrhous, or sclerosing, lymphoblastoma." This terminology would indicate a relationship with other lymphoblastic diseases, such as lymphosarcoma and

lymphoid leukemia, a part of the subject which is reviewed in the section on classification and relationships. The claim has been definitely made that the lymphoblast, as typified by the pale cells of the so-called germinal centers, is the offending element, the fibrosis and the polymorphic histologic picture being a reaction to this stimulant or to other secondary stimuli (Tsunoda).

Symmers gave his opinion that the disease is primarily granulomatous but that it may undergo malignant transformation, and that it has its origin in the bone marrow. Dietrich described it as a granulomatous lymphosarcoma. Scala believed it to be an intermediate form between a neoplasm and a granuloma, a theory also held by others. He stated that while epithelioid cells and histiocytes suggest granuloma, the Sternberg giant cells with their active reproductive processes are analogous to those of the hemolymphopoietic system and to those of the blastomas; the stroma is developed in symbiosis with the parenchyma.

Medlar recently suggested another cellular origin, namely, from the progenitors of the megakaryocytes, and placed the primary lesion in the bone marrow, the lesions outside of the marrow being metastatic tumors. He emphasized what he regarded as the predominant phase of lymphogranuloma by designating the disease as "megakaryoblastoma." This would suggest a close genetic relationship with the myeloid leukemias and the erythroblastic dyscrasias. His views, especially those concerning the derivation of cell types, are original.

Twort, in a large series of cases, tried many methods of investigation (direct examination for vegetable and animal parasites, examination of apparently healthy organs for protozoa, injection of lymphogranuloma filtrates and of bacteria into animals, sensitization experiments, attempts to produce specific antibodies in animals, examination of blood, other body fluids and excreta of both patients and inoculated animals, bacteriologic investigations, etc.). He concluded that "so invariably did the different experimental procedures we adopted lead to nothing that one might be dealing with a new growth instead of what is generally accepted to be granuloma."

I wish here to call attention to the relation of age and sex to the incidence and progress of the disease. Bunting suggested the importance of this relationship, and Gemmell stressed the probable effects of ovarian hormones. From a study of the age of the patients in a large number of cases taken from the literature and from my own experience, a striking curve may be drawn. The curve shows an initial rise up to the age of 5 or 6 years, with a gradual decrease as the age of puberty is reached; between the ages of 11 and 15 years the cases are much less numerous; this period is followed by a sharp elevation of

the curve. This, together with the established preponderance of male over female patients, seems to link the disease with growth and sex development or function. I feel that these facts concerning age and sex must be considered as strongly entering into and forming a part of the problem of etiology.

### TRANSMISSION

Transmission of Hodgkin's disease has never been accomplished by any method. Lesions that are practically indistinguishable from the classic picture have been produced in animals; yet the progressive development characteristic of the disease is always lacking. The clinical picture with inevitable termination in death has not been produced. Attempts at transmission may be outlined as follows: (1) injection of emulsions of lymph nodes or other tissue; (2) surgical implantation of nodes; (3) injection of various bacteria and fungi recovered from the patient; (4) injection of the patient's or the animal's blood or urine. The results obtained have been far from satisfactory, regardless of the method.

Little is to be gained in a review of this kind by a lengthy citation of inoculation experiments. The work of Bunting, Tyzzer, Cunningham and McAlpin, de Leon and Reyes, and Longcope on monkeys and apes has uniformly given negative results. Stewart and Dobson, and especially Twort, made extensive investigations, with negative results. Wachsmuth described the changes occurring in transplanted normal lymph nodes, noting early central necrosis, followed by cellular infiltration and proliferation of connective tissue, with complete disappearance of the architecture. As these are some of the changes usually described in connection with the implantation of Hodgkin's nodes they carry considerable significance.

Tyzzer implanted a piece of a node under the patient's own skin. It remained for ten days and then entirely disappeared. Simmons and Benet commented on this, suggesting that "a fragment of sarcoma or carcinoma treated in a like manner would probably have grown. This fact is rather against the tumor theory." More observations are necessary.

Twort produced local inflammatory nodules, believed to be due to toxins present in the injected tissues. Filtered emulsions of these cells led to no nodular formations, and incubation of the tissue with certain serums rendered them innocuous. Coyon and Brun asserted that they transmitted a "virus" by way of the blood stream which produced the histologic features of the disease in a guinea-pig. Tixier, in discussing this, suggested that great prudence must be exercised in the interpretation of such lesions, as they may be only a special form of tuberculosis. Loeper and Lemaire injected the blood and urine of

patients into guinea-pigs and concluded that they are specifically noxious to these animals. The lesions produced, while not the specific lesions of lymphogranuloma, could not be produced by the blood and urine of normal human beings. Sacquépée, Liegeois and Codvelle obtained histologic appearances resembling Hodgkin's disease in guinea-pigs by the injection of human material.

Numerous attempts have been made to transmit the disease by the injection of bacteria and fungi recovered from patients by culture. Here also the results may be considered as inconclusive. Grumbach obtained interstitial pneumonitis with suggestive pathologic features in guinea-pigs by the injection of an organism isolated from the blood during an acute phase; he also reported lesions resembling those of Hodgkin's disease following the injection of a peculiar diphtheroid bacillus. Busny claimed to have produced lesions similar to those of lymphogranuloma by the injection of peculiar acid-fast and coccoid organisms. These organisms could be found in all the tissues of the patient, and Busny believed that lymphogranuloma might be established as a generalized bacteremic infection. A series of passages of diseased splenic tissue appeared to increase the virulence in animals, the organisms mentioned being recovered in each case.

Histologic pictures which at times rather closely resemble that of lymphogranuloma may be produced by benzene, tar, actinomycetes, tuberculosis and syphilis, according to Brandt. Mueller cited the production of a polymorphocellular sarcoma by Kopsch, who fed the larvae Rhabditis pellio to frogs.

Vasiliu and Irimoin made numerous attempts to transmit the disease, and Sternberg mentioned that Vasiliu had obtained results that seemed to support strongly his belief in the tuberculous nature of lymphogranuloma. Medlar called attention to the close resemblance between the lesions of lymphogranuloma and those of avian tuberculosis. Schütt also noted the resemblance to Hodgkin's disease of tuberculosis occurring in guinea-pigs that had been inoculated with lymphogranulomatous material.

Concerning the congenital or hereditary transmission of the disease in man, the evidence is meager. Priesel and Winkelbauer cited one of the most remarkable cases in the history of the disease. Two weeks before the end of a normal pregnancy a diagnosis of lymphogranuloma was made by biopsy. The child was delivered normally, but it soon became ill, presenting enlarged nodes which were diagnosed as lymphogranuloma microscopically. It died shortly thereafter. Arkin reported 3 cases in a family, occurring in the father, a son and a nephew. Several cases have been reported in which women with the disease were delivered of perfectly normal children. Gemmell made an

extensive study of pregnancy in Hodgkin's disease; and in 57 cases he mentioned no instance of transmission to the offspring. Allan and Blacklock cited the cases of 2 brothers with Hodgkin's disease.

### BACTERIOLOGY

The bacteriology of Hodgkin's disease presents confusing and variegated findings, none of them generally accepted as etiologic.

Dreschfeld, in 1892, was the first to describe a bacillus in connection with the disease. Delbet, in 1895, reported another bacillus. Bramwell may also be cited as an early worker in the field. Abram, in 1898, was one of the first to recover an organism from the blood—a gram-negative micrococcus. He cited the early literature: Klebs (a bacillus); Weigert (acid-fast bacilli in the nodes); Kelsch and Vaillard (a coccoid bacillus in a leukemia); Traversa (streptococci in the blood); Grossi (streptococci in the blood); Lannois and Groux (Staphylococcus aureus). Abram believed that the micrococcus was a secondary invader and that the enlarged nodes decreased in size during the period of secondary infection, to enlarge again when the organisms disappeared from the blood.

Various types of cocci have been cultivated. Rosenow stated that "cocci predominate in the more recently enlarged glands." Fox and also Schütt found a large diplococcus. Cordier, Levy and Nové-Tosserand obtained an enterococcus from the blood. Streptococci were reported by Mathes and also by Miller, who interpreted his finding as a preagonal invasion. Cunningham stated that "staphylococci and streptococci may give rise to a picture simulating Hodgkin's disease histologically, either by direct infection or as an irritative reaction." Litterer, finding Staphylococcus albus in 4 cases, believed that it had something to do with the exacerbations. Haythorn, Robinson and Johnson described an unusual reaction produced in animals by the injection of a monilia recovered from a patient. They described the condition as Hodgkin's disease with secondary infection by the monilia. Twort found curious bodies resembling the spores of a fungus (Alternaria?) in 5 per cent of his cases; he found streptococci and diphtheroid and tubercle bacilli occasionally. Grumbach did considerable work on a bacillus resembling Corynebacterium diphtheriae and differing from the various pseudodiphtheria bacilli. He made no claim as to etiology, but stated that the bacterium on inoculation into animals produced lesions almost like those of Hodgkin's disease. The organism appeared coccoid at first, then like C. diphtheriae, and then irregular.

Busni described a curious organism which began as an acid-fast rod and changed to a coccus. The same organism was found in cases of mycosis fungoides. Grandclaude, Lesbre and Foulon, by delayed

anaerobic cultures of lymph nodes of patients with the disease obtained organisms similar to Busni's (bacillary and coccus forms). They placed them in the group studied by Haudroy and by Haudroy and Lesbre, believing that they played the part of biohormones in abnormal cell proliferation, and they did not assign them an etiologic rôle.

Blood cultures have often given negative results (Cunningham; Barron; MacNalty). Splenic punctures gave negative results on two occasions (MacNalty). Direct examination of blood films for parasites has never shown any (MacNalty, and others). Twort examined the feces, finding no Protozoa which could be associated with the disease. He also was unable to demonstrate toxins or bacteriophages.

In my own experience diphtheroid bacilli and cocci have been found. Recently a peculiar streptococcus was obtained after one month's incubation on Kendall's new medium. Diphtheroid bacilli have often been recovered from excised nodes. The rôles of various diphtheroid bacilli, especially that of Corynebacterium hodgkini (de Negri and Mieremet; Bunting), are well outlined in Simonds' review. While final decision is reserved, it is generally held that these organisms are not etiologic. Kusunoki held the opinion that they are more abundant in cases in which the growth of the peculiar large cells is prominent and in which giant cells are numerous, and less numerous in markedly fibrotic nodes. He gave a considerable bibliography. Other papers on the subject have been published by Rhea and Falconer, Simon and Judd, Steel, Verploegh, Ayrosa, Hirschfeld, Rosenfeld, Dietrich, Simonds, Luce, Fox, Cunningham, Henrici, Mellon, Bunting, and de Negri and Mieremet.

*Ameba.*—Kofoid's theory that an ameba is etiologically related to Hodgkin's disease has neither been generally discussed nor accepted. Barron, however, expressed his belief in the possibility of the etiologic agent being an animal parasite and cited reasons therefore. He stated that while Kuczynski and Hauck's theory (that the disease is an infection by a fungus or that the inclusion bodies in the Sternberg cell are plant or higher bacterial forms) is questionable, "the indefinite pleomorphic cellular inclusions which they describe correspond much more closely to animal parasites or the cellular reactions to animal parasites," and that such animal parasites could conceivably fulfil all the requirements of an etiologic factor in Hodgkin's disease. Coffen, in discussing Barron's paper, supported the idea of an animal parasite. Both of these authors argued for this theory on the following grounds: (1) Practically all known chronic relapsing fevers are caused by animal parasites (malaria, trypanosomiasis, relapsing fever, kala-azar, etc.); (2) eosinophilia is commonly associated with diseases caused by animal parasites (trichiniasis, filariasis, trypanosomiasis and helmin-

thiasis); (3) tuberculosis and other known bacterial infections never produce any definite eosinophilia, unless by allergic reactions, as in bronchial asthma, and (4) the fact that Hodgkin's disease is not transmissible to animals is more in keeping with the possibility that it is caused by an animal parasite.

In summary, it may be said that, by the methods of the present day, no organism or parasite can be shown to produce the disease.

*(To be Concluded)*

# Notes and News

**University News, Promotions, Resignations, Appointments, etc.**—R. A. Webb has been appointed professor of pathology in the school of medicine for women at the University of London.

As previously noted, a department of forensic medicine has been established in the University and Bellevue Hospital Medical College, New York, with the following staff: Charles Norris, professor of forensic medicine; Alexander Gettler, professor of toxicology; Douglas Symmers, professor of gross pathology; Harrison S. Martland, associate professor of forensic medicine; Thomas A. Gonzales, assistant professor of forensic medicine, and Armin V. St. George, assistant professor of gross pathology. Six lectures dealing with the relationship between the physician and the medical examiner's office and other medicolegal topics will be given all fourth year students. The main instruction in forensic medicine, however, will be in the form of elective courses and in graduate work. The department is linked with the medical examiner offices of the City of New York and of Essex County, N. J.

Carl F. Kleine has succeeded Fred Neufeldt as director of the Robert Koch Institute for Infectious Diseases in Berlin.

Herbert U. Williams, professor of pathology in the University of Buffalo, has been granted leave of absence for travel until the middle of March, 1934. During his absence the work in pathology will be directed by a committee from the faculty.

**Committee for Survey of Research on the Gonococcus and Gonococcal Infections.**—This committee has been formed by the Division of Medical Sciences of the National Research Council in cooperation with the American Social Hygiene Association. Its purpose is to collect, analyze and collate the facts already established and the efforts now in progress to add to knowledge of the gonococcus and gonococcal infections, especially as regards bacteriology, pathology, immunity, the mechanism of infection and some of the forms of therapy. Attention will be concentrated chiefly on work done in the United States. At the close of the preliminary survey the committee, with the assistance of a conference of experts, will compile a report with the object of stimulating interest in the study of the gonococcus, of providing a point of departure and of suggesting promising leads for further investigation. The survey will cover the literature, but it is hoped that unpublished work and studies which were incomplete or the results of which were inconclusive may also be included. Dr. Stanhope Bayne-Jones, chairman, earnestly invites the cooperation of workers interested in this field. Headquarters have been established at Room 1101, 450 Seventh Avenue, New York, where communications and reprints will be welcomed.

## CORRECTION

In the abstract of an article by Drs. David P. Seecof, Charles R. Linegar and Victor C. Myers, entitled, "The Difference in the Creatine Concentration of the Left and Right Ventricular Muscles of the Heart," which appeared as part of the proceedings of the American Society for Experimental Pathology in the August issue (ARCH. PATH. **16**:308, 1933), an error occurred in the fifth and sixth lines of the second paragraph. The statement "per hundred cubic centimeters of blood" should have read "per hundred grams of muscle."

# Abstracts from Current Literature

## Experimental Pathology and Pathologic Physiology

SPLENECTOMY IN BILE FISTULA DOGS (BILE PIGMENT OVERPRODUCTION, ANEMIA AND INTOXICATION). F. B. QUEEN, W. B. HAWKINS and G. H. WHIPPLE, J. Exper. Med. **57**:399, 1933.

A splenectomized dog can be kept anemic for months or years in perfectly good condition. A dog with a renal biliary fistula, on a suitable diet, can be kept in perfect health and activity, with normal weight, for years. When splenectomy and a biliary fistula are combined, one invariably observes, after a latent period, a striking reaction, with an enormous overproduction of bile pigment, definite anemia and finally death from anemia or from hemorrhage in the tissues. The spleen is essential for life in an animal with a biliary fistula, and this suggests an association of the spleen with the internal metabolism of the body. The spleen and bile together are essential for the normal metabolism of pigment. It is thought that the bile salts play some obscure rôle in this reaction. It is difficult to explain the excess of bile pigment as coming from hemoglobin built up from the usual diet factors which, in our experiments, were well standardized. It is suggested that the body can synthesize the pyrrol aggregate (four pyrrol rings). There is some evidence that the liver can build up bile pigment directly from "building stones." It seems necessary to postulate one or the other mechanism, and they do not seem unlike in the final analysis, as both bile pigment and the pyrrol aggregate contain four pyrrol rings. Possibly both reactions may take place under these conditions.

AUTHORS' SUMMARY.

CELLULAR MECHANISMS OF RENAL SECRETION. J. R. OLIVER and E. M. LUND, J. Exper. Med. **57**:435 and 459, 1933.

The secretion of neutral red reproduces the variations which are observed in the mitochondrial apparatus of the renal tubule cells of animals living under natural conditions. The tubular absorptive processes concerned with water, salts and sugars do not produce these effects. The changes in the mitochondria consist of alterations in both the structure and the constituents. These have been shown to be not merely phenomena concomitant with secretion, but a determining factor in one part of this process, namely, in the concentration of the dye within the cell.

The elimination of neutral red by the renal epithelium is a composite process, consisting of direct and indirect secretion. The mechanism controlling direct secretion is concerned with the permeability of the two cellular membranes. These membranes may be affected independently in the direction of either an increased or a decreased permeability, with a corresponding increase or decrease in the elimination of the dye. The mechanism controlling indirect secretion is concerned with the mitochondrial apparatus of the cell. By means of change in form and constituent substance, the dye is concentrated within the cell and is slowly eliminated. Direct secretion, depending on the condition of sensitive membranes, is easily disturbed. Such disturbances account for the wide variations in the elimination of dye observed in the functioning of abnormal kidneys. Indirect secretion, depending on the simpler factor of the solubility of the dye in the protoplasmic constituents, continues even when the cells are severely damaged.

AUTHORS' SUMMARIES.

EPITHELIAL REPAIR IN RECOVERY FROM VITAMIN A DEFICIENCY. S. B. WOLBACH and P. R. HOWE, J. Exper. Med. **57**:511, 1933.

In vitamin A deficiency, the stratified keratinizing replacement epithelium is morphologically identical in all locations. All the cells of the lowermost layer of

the replacement epithelium have proliferative power, as in the stratum germinativum of the epidermis. In recovery, in spite of the complete morphologic masking, the epithelium in each region returns to its normal type. The important histologic features of repair involve removal of the layers of cells irreversibly differentiated toward keratinization and direct differentiation of the stratum germinativum toward the normal type. These take place simultaneously. The histologic sequences observed in the removal of cells above the stratum germinativum indicate that autolysis, as shown by vacuolar degeneration, and heterolysis, as shown by leukocytic infiltration, are involved. The cycle of vitamin A deficiency, metaplasia and recovery affords an experimental method available for the correlation of nuclear chromatin and types of cytoplasmic activities. AUTHORS' SUMMARY.

THE RELATION OF MANGANESE TO LIVER CHANGES. P. K. RAO, Beitr. z. path. Anat. u. z. allg. Path. **87**:599, 1931.

Acute manganese poisoning in rabbits produced severely necrobiotic processes in the periphery of the lobules of the liver, and, in general, death supervened before reparative proliferation occurred. Cirrhosis could not be produced. Chronic continuous manganese poisoning caused monolobular cirrhosis, with cell proliferation and an interstitial increase of the collagenic and argentophil fibers in the periportal area. Chronic intermittent manganese poisoning produced either no effect or a very minor degree of cirrhosis. W. S. BOIKAN.

## Pathologic Anatomy

A STUDY OF THE HEART IN HYPERTHYROIDISM. GEOFFREY RAKE and DONALD MCEACHERN, Am. Heart J. **8**:19, 1932.

Both the results of autopsy and the experimental material point to the fact that hyperthyroidism by itself produces no specific lesions in the myocardium. It is conceivable that the damage produced by physiologic wear and tear or by an associated infection or disease tends to be more accentuated in a person with hyperthyroidism than in a normal one. It is difficult to be certain whether or not the injury in cases such as those described by Fahr, Goodpasture and Lewis, and two in the present series, in which profound damage is present without any coexisting complicating disease, represents the effects of a toxin derived from the thyroid gland and circulating in the blood. The evidence points against the occurrence of a specific causal toxin producing specific myocardial lesions. It is felt that in the past too much emphasis has been laid on the morphologic changes in the myocardium, with consequent neglect of important alterations in the metabolism and function of the muscle fibers. In this connection attention may be drawn to the recent work on the glycogen content of voluntary and cardiac muscle in hyperthyroidism. It has been shown that in the experimentally produced disease no glycogen can be found in the myocardium microscopically or by chemical analysis. As a result of this, rigor mortis sets in immediately, a fact which the authors can abundantly confirm from their experimental experience. It is well known that the withdrawal of glycogen from cells normally well supplied with it renders them more liable to injury, to which they react by diminished function, structural change and death. This problem has been thoroughly examined in the case of the liver, and one may well believe that similar reasoning can be applied to the myocardium. It seems more than probable that a close examination of this physiologic problem and others will bring one nearer to an understanding of the cardiac abnormalities in hyperthyroidism. AUTHORS' SUMMARY.

THE HEART IN EXPERIMENTAL HYPERTHYROIDISM. FRANK R. MENNE, ROGER H. KEANE, ROBERT T. HENRY and NOBLE W. JONES, Am. Heart J. **8**:75, 1932.

Hyperthyroidism produced experimentally in rabbits for twenty-three days by means of (1) thyroxine, (2) thyroid and (3) desiccated human thyroid (from

patients having exophthalmic goiter) resulted in the following changes in the hearts: parenchymatous and fatty degeneration, histiocytic invasion, fraying of the muscle bundles and early fibrosis. Similar changes may be produced by cardiac overwork irrespective of the presence of an excess of thyroxine in the circulating blood, as is indicated by the results obtained on cutting depressor nerves and denuding the carotid sinuses of their investments in order to allow the heart to operate uncontrolled. There is no evidence in the literature to disprove the fact that a heart which is induced to work more rapidly, with an increased output in the presence of increased pressure and metabolism (as is true in hyperthyroidism), may not exhaust its nutrition and respond with morbid anatomic changes that may be erroneously ascribed to the pernicious influence of thyroxine on the myocardium.

AUTHORS' SUMMARY.

CONGESTIVE HEART FAILURE AND HYPERTROPHY IN HYPERTHYROIDISM. E. J. KEPLER and A. R. BARNES, Am. Heart J. **8**:102, 1932.

In 27 of 178 fatal cases of hyperthyroidism severe congestive failure of the heart occurred. Eighteen of these cases (67 per cent) were associated with coronary sclerosis, hypertension, acute or chronic pericarditis, rheumatic endocarditis or syphilis. In the remaining cases no cause for the congestive failure other than hyperthyroidism could be found.

AUTHORS' SUMMARY.

SPONTANEOUS RUPTURE OF THE AORTA. OSKAR KLOTZ and WINIFRED SIMPSON, Am. J. M. Sc. **184**:455, 1932.

The authors analyze five cases of so-called spontaneous nonsyphilitic rupture of the aorta. The underlying process consisted of a peculiar noninflammatory degeneration of the media, affecting the muscle and elastic fibers and similar to the lesions which precede the development of dissecting aneurysms. This degenerative process in the aorta seems to have been due to a variety of factors, viz., bacterial toxins, exogenous poisons, such as nicotine and epinephrine, toxic products of deranged nitrogen and glycogen metabolism and possibly certain dietary deficiencies. In one case there was thrombosis of the nutrient arteries of the aortic wall. The peculiar medial degeneration without spontaneous rupture or dissecting aneurysm is found with increasing frequency with advancing age, either as a diffuse process or in patchy distribution throughout the aorta.

SANDER COHEN.

MELANOMA STUDIES: I. THE DOPA REACTION IN GENERAL PATHOLOGY. GEORGE F. LAIDLAW, Am. J. Path. **8**:477, 1932.

The dioxyphenylalanine reaction was introduced by Bloch, the dermatologist of Zurich. Dioxyphenylalanine is a phenol which oxidizes readily to melanin. Melanoblasts and myelogenous leukocytes hasten the oxidation and stain black from the accumulation of dioxyphenylalanine melanin in or on them. The blackening of the cell constitutes a positive reaction. Bloch holds that the conversion of dioxyphenylalanine to melanin is the work of a ferment of the reacting cell. He holds further that this oxydase is the natural melanin-producer of mammalian skin.

Laidlaw accepts Bloch's explanation as the best working hypothesis of the production of melanin, both normal and pathologic, in mammalian skin. He finds that the abundance of cells giving a positive reaction to dioxyphenylalanine is parallel with the activity of melanin production. For instance, if leukocytes are excepted, cells giving positive reactions are found only in tissues where melanin is being produced or where it can be produced under appropriate stimulation. When melanin is being formed in excess, as in Negro skin, in irradiated Caucasian skin, in pigmented moles and in the pigmentation of Recklinghausen's disease, the number of the positively reacting cells and the complexity of their dendrites are increased. When the power to form melanin is congenitally absent, as in the white skin of animals, or has been lost, as in vitiligo of Negro skin, no such cells are found. When the production of melanin is resumed, as in the repigmentation

of vitiligo or of scars, cells giving positive reactions always reappear before the production of melanin. These cells are found also in mucous membranes of ectodermal origin, such as the conjunctiva and the mucosae of the mouth, lips, gums, external genitals and anal canal, all frequent sites of melanin formation. An unexplained phenomenon is the constant occurrence of dioxyphenylalanine-positive cells without pigment formation in the acanthoses.

The melanin-bearing cells of the derma never react to dioxyphenylalanine. They contain no ferment and are thought to be phagocytes, not melanoblasts. The only exception is the pigmented cell, a true mesodermal melanoblast and the sole source of melanosarcoma of the skin.

The dioxyphenylalanine reaction has no relation to malignancy. The cells of ordinary sarcoma and carcinoma never give the reaction. In some carcinomas, a few cells that give a positive reaction are found scattered among the epithelial cells, but they are of no significance. In melanosis coli, the melanin-bearing cells give a negative reaction, confirming the orthodox opinion that these cells are phagocytes, not melanoblasts.

The author rejects the common opinion that mammalian melanoblasts are necessarily dendritic like those of amphibia and of reptiles. He shows that in normal mammalian skin, in pigmented moles and in malignant melanomas, the melanin-producing cells and phagocytes alike may assume any shape, round or cuboidal, without dendrites or highly dendritic. The shape of the cell has no relation to its power of producing melanin.

The author confirms Bloch's contention that the reaction to dioxyphenylalanine and the silver reaction of melanin-bearing cells are totally different. Silver blackens melanin wherever it is found, in both melanoblasts and phagocytes and in the interstitial tissue. Leukocytes being excepted, dioxyphenylalanine blackens only the melanoblasts and these only when they contain an active ferment. Pigmented moles and melanomas contain many tumor cells which do not react to dioxyphenylalanine. These are latent melanoblasts which may at any moment resume their melanin-producing function, in which event they will give a positive reaction.

The paper includes photomicrographs showing reactions to dioxyphenylalanine and a full bibliography. A résumé of the material on the reaction and on the technic was published in the *Anatomical Record* (**53**:399, 1932).

GEORGE F. LAIDLAW.

PRODUCTION OF NONFATAL VASCULAR SCLEROSIS IN RABBITS BY MEANS OF VIOSTEROL (IRRADIATED ERGOSTEROL). T. D. SPIES, Arch. Int. Med. **50**:443, 1932.

In the experiments reported the administration of repeated, massive doses of viosterol produced severe and persistent sclerosis of the aorta and renal vessels. This phenomenon was associated with deposition of calcium within the parenchyma of the lungs and kidneys. It is worthy of emphasis that soon after the final dose of viosterol was administered all the animals regained their normal appetite and body weight. They continued to have normal renal function. At the termination of the experiment, they appeared in the best of health. In general, the vascular process was one of extensive sclerosis with hyalinization and calcification of the media. The pulmonary changes consisted of calcification of the trachea, the bronchial cartilages and, at times, the bronchial and alveolar epithelium. Deposits of calcium were absent in the pulmonary vessels. The renal arteries, arterioles, tubules and glomerular capsules were hyalinized and calcified. The lesions were slightly less prominent than those of animals that were allowed to die from poisoning with viosterol. However, they are considerably more extensive than the lesions produced by some other workers who allowed the animals to die from massive doses of viosterol. Three and a third months after their production the lesions were extreme, and I think that they represent about the maximal degree of involvement compatible with return to apparent health. In many of the lesions the apparent proportion of hyalinized tissue to microscopically visible calcium was greater than in comparable lesions in the previous experiments; this suggests

that some of the calcium had been reabsorbed during the three or four months after the cessation of medication. Naturally, the vascular deformity would be expected to remain despite any tendency toward reabsorption of the calcium. The vascular sclerosis produced in these experiments was not the result of spontaneous atherosclerosis, which sometimes occurs in older rabbits. Also, the experimental lesions did not in any way resemble the changes found in the aortas of rabbits following the administration of cholesterol or nonirradiated ergosterol. This study seems to show a method of producing permanent severe sclerosis of the aorta and renal vessels.

AUTHOR'S SUMMARY.

STATUS MARMORATUS, ETIOLOGY AND MANNER OF DEVELOPMENT. K. LÖWENBERG and WILLIAM MALAMUD, Arch. Neurol. & Psychiat. **29**:104, 1933.

Status marmoratus is characterized by the appearance in the corpus striatum of stripes of myelin which form a dense network containing in its meshes lighter islands of degenerated nerve tissue, for the most part replaced by glia. The authors report four cases, three of which were studied histologically. Formation of scars of glia tissue and their myelinization took place in the corpus striatum, optic thalamus and cortex. The lesions were rather diffuse. In one case the process spared the basal ganglions and was confined to the cortex. The process is, according to the authors, inflammatory and not a developmental anomaly.

G. B. HASSIN.

THE BRAIN IN A CASE OF MOTOR APHASIA IN WHICH IMPROVEMENT OCCURRED WITH TRAINING. H. DOUGLAS SINGER and A. A. LOW, Arch. Neurol. & Psychiat. **29**:162, 1933.

Right hemiplegia including the face developed in a woman one day following a difficult confinement. The paralysis was accompanied by aphasia, with inability to talk but with apparent understanding of speech. Two years after the stroke the patient was taught to pronounce simple, monosyllabic words, and later more complicated words; she was also trained in using the extremities. Death occurred twenty-five years later. Necropsy revealed a cavity on the left side involving the second and third frontal convolutions, which extended to the corpus striatum. Microscopic studies revealed an old process of destruction of the areas which preside over the function of speech; yet the latter improved considerably with persistent training.

G. B. HASSIN.

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD. N. W. WINKELMAN and CHARLES DAVISON, Arch. Neurol. & Psychiat. **29**:317, 1933.

The authors studied the changes in the spinal cord in twenty-five cases of pernicious anemia with a view to determining whether such changes are inflammatory, degenerative or of some other origin. In five cases, in some of which the duration of the disease was from four to seven years, the blood vessels exhibited perivascular infiltration. The type of the infiltrating cells was determined by using differential stains—sudan IV, for instance, for fat, and a nuclear stain, such as the Unna-Pappenheim stain, for lymphocytes or plasma cells. The predominance of fat in subacute combined degeneration of the cord shows it to be a degenerative process; the prevalence of lymphocytes and plasma cells indicates inflammation. The presence of both, as in dementia paralytica, denotes a combined process (inflammatory and degenerative).

G. B. HASSIN.

NERVE DEGENERATION IN POLIOMYELITIS. HERMAN CHOR, Arch. Neurol. & Psychiat. **29**:344, 1933.

Chor studied, by means of a slight modification of the pyridine-silver method of Ranson, the changes in the motor nerve endings as they occur in experimental poliomyelitis of monkeys. He contrasted the changes with those in normal animals

and in monkeys in which the nerves had been cut. The changes in the muscular nerve endings in poliomyelitic monkeys were found to be analogous to those obtained after experimental sectioning of the nerves: Swelling and thickening of the terminal arborizations of the axons occur, followed later by fragmentation of the neurofibrils and swelling and breaking up of the myelin and axons with final granular transformation of the motor end-plates. The difference is that in poliomyelitis the changes, which begin with the onset of the paralysis, are not as diffuse as those in experimentally produced degeneration (by nerve section). There are in poliomyelitis many normal looking end-plates mixed with some which exhibit various stages of degeneration. Regenerative phenomena occur late, two months after the lesion. The variety and the degree of the changes in the end-plates depend on the condition of the ventral horn cells, being secondary to it. That they are not primary, that is, are not, like the changes in the ganglion cells, due to the direct action of the poliomyelitic virus, is proved by the fact that saturation of the muscles themselves with the virus and through them of the motor nerve endings failed to produce in the latter demonstrable histologic changes.

G. B. HASSIN.

ABSCESS AND THROMBOSIS OF THE SUPERIOR LONGITUDINAL SINUS. GEORGE B. HASSIN, Arch. Neurol. & Psychiat. **29**:359, 1933.

In a man in whom an intracranial streptococcic infection of sixteen months' duration developed following a mastoid lesion, necropsy revealed an abscess of the longitudinal and sagittal sinuses and thrombosis of the frontal part of the former. It was possible to follow the successive stages of the transformation of the abscesses into a connective tissue scar and to demonstrate the rôle played by various mesodermal elements, especially the histiocytes and fibroblasts. The thrombus was separated from the dura by elastic fibers, and over the lateral sinuses the dura was studded by small abscesses. The pia showed no changes; the arachnoid exhibited masses of mesothelial cells, and in the brain, especially in the frontoparietal region, neuronophagia and satellitosis were present. Signs of hydrocephalus or hydrops of the brain were absent, which speaks against the theory that the spinal fluid, after passing through the pacchionian bodies, is received by the longitudinal sinus for final absorption. Failure to do this should, if the theory is correct, invariably lead to external and internal hydrocephalus—which were absent; neither were changes present in the pacchionian bodies.

AUTHOR'S SUMMARY.

ADDISON'S DISEASE WITH SO-CALLED ATROPHY OF THE ADRENAL CORTEX. G. LYMAN DUFF and C. BERNSTEIN, Bull. Johns Hopkins Hosp. **52**:67, 1933.

Five cases of Addison's disease, in four of which the patient had been treated with extract of suprarenal cortex, are reported. All of the patients showed more or less complete "atrophy" of the suprarenal cortex. The destructive process in the suprarenals consisted of a progressive necrosis of cortical cells with collapse of the stroma. In two cases there was regeneration of cortical tissue. The medulla was affected much less, usually showing only a slight increase in the density of the fibrous framework and some shrinkage of the medullary cells. Lymphocytic infiltrations were constantly present in the suprarenal medulla and among the remnants of cortical tissue. Lymphocytic infiltrations in various situations constituted the most constant findings in association with the suprarenal lesions. Marked hyperplasia of lymphoid tissue was not present. No lesions were found for which the treatment with extract of suprarenal cortex could be held responsible. Consideration of the possible etiologic factors in the suprarenal lesions leads to the conclusion that a circulating toxin of unknown origin and nature was probably the causative agent. A brief account is given of observations on four cases in which the early stages of destruction of the suprarenal cortex were found but no clinical evidence of Addison's disease. The findings indicated that the primary suprarenal lesion is in the cortex and that the three zones of the cortex differ in their susceptibility to damage.

AUTHORS' SUMMARY.

CONGENITAL ATRESIA OF THE SMALL INTESTINE. F. LAESSING, Arch. f. Kinderh. **97**:1, 1932.

This article includes a review of the literature, a report of a case and a discussion of the subject. In a 3 day old child, born at full term, who died of icterus and bronchopneumonia, the stomach, duodenum and proximal 20 cm. of the jejunum were dilated. Twenty centimeters from the duodenojejunal flexure, the bowel was narrowed and twisted on its axis, and a swollen, tumid loop passed through a small, smooth-edged opening in the mesentery and hung free in the abdomen below. Histologically there were two bandlike constrictions, with loss of the lumen, mucosa and submucosa. The lumen between was lined by normal mucosa and contained mucus. The distal portion of the bowel was dilated and contained whitish masses. At the point of narrowing there were hypertrophy of the muscular coats, proliferation of connective tissue and cells containing blood pigment. The author does not consider that there was enough evidence of damage to account for volvulus due to peristaltic activity, nor was the nature of the occlusion suggestive of an arrest of epithelialization. He believes that the condition was due to trauma, "in the broadest sense of the word," occurring before the fifth month of fetal life. The nature of the trauma is an open question.

J. STEWART.

CENTRAL TUBERCULOUS MYELITIS. M. B. SCHMIDT, Beitr. z. path. Anat. u. z. allg. Path. **87**:314, 1931.

In a 58 year old patient with the clinical appearance of having a tumor of the cord there was discovered a syringomyelia-like tuberculous lesion. There was an obturating tuberculous arteritis with secondary, noncaseating ischemic myelomalacia.

W. S. BOIKAN.

EFFECT OF UNILATERAL INTRA-AURICULAR RISE IN PRESSURE ON THE AURICULAR SEPTUM. H. MILLER, Beitr. z. path. Anat. u. z. allg. Path. **87**:365, 1931.

A long continued rise of pressure in one auricle leads to thinning and bulging of the membranous part of the auricular septum toward the side of lower pressure. In mitral stenosis this bulge may assume aneurysmal proportions. With a rise of pressure on the right side from failure of the right side of the heart, this bulge disappears. The author found one case of emphysema with aneurysmal dilatation into the left auricles. He further points out that a persistent eustachian valve forms, together with the atrial septum, a runway which directs the blood from the inferior vena cava toward the foramen ovale and may be the pertinent factor in the maintenance of the patency of the foramen and in the genesis of paradoxical emboli.

W. S. BOIKAN.

PEPTIC ULCER IN MECKEL'S DIVERTICULUM. G. SCHAAFF, Deutsche Ztschr. f. Chir. **238**:78, 1932.

Gastric mucosa was found in six of fifty cases of Meckel's diverticulum, and occasionally in omphalomesenteric cysts and fistulas. Hydrochloric acid and pepsin have been found in such cases, which indicates normal gastric mucosa function as well as structure. The ulcers present were similar histologically to gastric ulcers, and in one case the free hydrochloric acid was 40 and the total 70. The clinical history so closely simulates that of gastric or duodenal ulcer that preoperative diagnosis is difficult or impossible. The aberrant gastric mucosa secretes simultaneously with the stomach, and therefore pain appears soon after meals and is relieved by the alkaline intestinal fluid. The most constant features of the condition are the massive hemorrhage, bright red and often dark stools, colicky pains and severe peritonitis if perforation occurs.

J. STEWART.

FATAL HEMORRHAGE FROM ESOPHAGEAL VARIX IN THE ABSENCE OF ABNORMALITY OF THE LIVER. J. NOCHIMOWSKI, Frankfurt. Ztschr. f. Path. **43**:463, 1932.

In two persons with esophageal varix the liver was normal and no cause for the varices was found.

RELATIONSHIPS BETWEEN LEUKEMIA AND GOUT. ARTHUR SCHULTZ, Virchows Arch. f. path. Anat. **280**:519, 1931.

In a case of gout with typical deposits of urates in the joints, tendon sheaths and bursae, there were extensive leukemic infiltrations in the liver, spleen, lymph nodes, bone marrow and kidneys, with an aleukemic blood picture. In leukemia the kidneys occasionally have deposits of ammonium urate in the form of spheroliths in the lumens of the collecting tubules, similar to so-called uric acid infarcts in the new-born. In gout, however, the kidney has in the interstitial tissue deposits of uric acid which change to sodium urate and become organized by foreign body granulomas. The latter picture was found in this case. A relationship between leukemia and gout is considered. Three methods for the histologic demonstration of uric acid and urates are presented.

PERRY J. MELNICK.

CYSTICERCUS IN THE BRAIN. P. HEILMANN, Virchows Arch. f. path. Anat. **286**:176, 1932.

In five thousand necropsies, Heilmann has encountered a cysticercus in the brain six times. In three of the cases the cyst was situated in the fourth ventricle and in one case, in the third ventricle; in all of these it was the immediate cause of death by occlusion of the foramen of Magendie or of the aqueduct of Sylvius. In the fifth case the cyst was racemose, involved the region of the sylvian fissure, and was not the cause of death. In the sixth case the cyst occluded the foramen of Monro and caused death. This case is reported in detail because the author was not able to find a recorded instance of occlusion of the foramen of Monro by a cysticercus, although the statement is made that such a condition occurs.

O. T. SCHULTZ.

ILEOCOLIC HERNIA. K. G. ROSCHDESTWENSKIJ, Virchows Arch. f. path. Anat. **286**:249, 1932.

In 1923 and 1924, K. Z. Jazuta, a professor at the University of Rostow, described in the human fetus from 60 to 70 mm. long a shallow pocket or depression of the mesial surface of the mesentery of the cecum, which he named recessus ileocolicus. It is present in 88 per cent of fetuses from 200 to 300 mm. long, in 78 per cent of fetuses from 300 to 520 mm. long, in 60 per cent of infants less than 1 year old, in 20 per cent of children from 1 to 5 years old and in 10 per cent of children from 5 to 10 years old. Jazuta saw the pocket only once in an adult; he expressed the belief that in that instance it might be the site of an extraperitoneal hernia. Such a hernia in an adult is described by Roschdestwenskij; it was found by chance during anatomic study.

O. T. SCHULTZ.

## Pathologic Chemistry and Physics

DETECTION AND DETERMINATION OF ORGANIC ACIDS IN BLOOD SERUM. H. BRUHL, Klin. Wchnschr. **12**:72, 1933.

Organic acids in 2 cm. of blood serum were determined by making a graph of the electrometric titration curves of the ultrafiltrate of the serum. The organic acids of serum are increased in pregnancy and in uremia; the acids in pregnancy, however, differ from those in uremia. Increases were also found in patients with convulsions and in patients on a ketogenic diet. A decrease in the organic acids

occurred in children with florid rachitis. A comparison of the arterial and venous blood of the brain showed that the organic acids disappear in the brain in tetany.

D. O. Rosbash.

Acid-Base Balance and Edema. O. L. E. de Raadt, Klin. Wchnschr. **12**:224, 1933.

Edema is due to a disturbance in the acid-base equilibrium of the blood and not to a lowering of the colloidal osmotic pressure of the blood by a decrease in proteins. The decrease in the serum protein of the blood causes alkali deficiency through loss of sodium bound to the protein and through loss of the buffer action of the protein. The resulting acidosis is not compensated by the kidneys. Edema accompanying decompensation of the heart does not differ from nephritic edema. There is acidosis because of circulatory obstruction, a lowered excretion of carbon dioxide and a decrease in the formation of ammonia by the kidneys. The end-products of metabolism are acid (organic acids and carbon dioxide). In cardiac disease the acidosis is greatest when circulatory disturbances are maximum, and as a result edema appears first in the lower extremities. In edema accompanying heart disease the blood contains as much ammonia as it does in nephritic edema. The change of permeability of the capillaries in edema is a result and not a cause, since the formation of ammonia in the tissues alters the permeability of the capillaries.

D. O. Rosbash.

Radioactivity of Pathologic Tissues After Intravenous Administration of Thorium. G. Joannović, D. K. Jovanović and X. Chahovitch, Virchows Arch. f. path. Anat. **287**:127, 1932.

Previous experiments on rabbits showed that after the intravenous administration of radioactive thorium salts, the liver, spleen, epithelium of the lungs and bone marrow become radioactive. Experimentally produced tar cancers and papillomas exhibited no radioactivity. To determine whether normal tissues that undergo pathologic alteration retain their ability to store radioactive substances, a small series of experiments was performed. Two dogs which had been rendered diabetic by resection of the pancreas received radioactive thorium intravenously. In other dogs parenchymatous changes were brought about by phosphorus poisoning. The animals and their controls were killed twenty-four hours after the injection of thorium. No change was noted in the radioactivity of the liver, the spleen and the epithelium of the kidney and lung in the animals in which pathologic changes had been produced. The determination of radioactivity was not quantitative, but was judged by the ability of the tissues to affect the photographic plate.

O. T. Schultz.

Enzyme Content of the Pancreas. J. Baló and L. Lovas, Virchows Arch. f. path. Anat. **288**:326, 1933.

The enzyme content of the pancreas was determined in a series of seventy necropsies on persons who died of a variety of diseases. In twenty only lipase and trypsin were found; in the remaining fifty diastase was also found. In general the three ferments varied pari passu with each other. In sepsis, trypsin was reduced to a greater degree than were the other two ferments. In wasting, cachectic diseases, the three ferments were reduced. Lipase was increased in two cases with fat necrosis; Baló and Lovas suggest that increased lipase content may predispose to fat necrosis.

O. T. Schultz.

Phanerosis of Fat. N. M. Nikolajew and S. Lodyshenskaja, Virchows Arch. f. path. Anat. **288**:554, 1933.

A series of simple but ingenious experimental technical procedures for the visualization of cellular lipoids led Nikolajew and Lodyshenskaja to some important

conclusions relative to lipoid metabolism. They believe that the tissue cells may absorb preformed lipoids directly from the blood and tissue fluids; this is the usual normal physiologic process. Or the cells may take up protein-lipoid complexes, which may be acted on by intracellular ferments, the lipoid fraction becoming stainable by the usual methods or after treatment with ammonium chloride. The second process is the one that occurs under pathologic conditions. Toxins, poisons and other noxious factors lead to the liberation of protein-lipoid complexes, which are taken up by tissue cells. In the latter, fermentative destruction of the complex may have diverse effects on the cell. The water and protein balance of the cell may be disturbed, a condition that manifests itself morphologically as parenchymatous, hyaline or vacuolar degeneration. Or the lipoid element of the complex may be visualized, a state that evidences itself morphologically as fatty degeneration. Nikolajew and Lodyshenskaja accept Ciaccio's classification of the cellular lipoids into anabolic and histogenous, but subdivide the anabolic lipoids further into the free and the bound. Under both normal and abnormal conditions, endogenous lipoids derived from broken-down red corpuscles and other cells play an important part in cellular metabolism.

O. T. SCHULTZ.

PHYSICOCHEMICAL CHANGES OF PARENCHYMATOUS DEGENERATION. V. UHER, Virchows Arch. f. path. Anat. **288**:562, 1933.

In this continuation of previously reported studies of the physicochemical changes of parenchymatous degeneration, Uher used suspensions of liver cells and determined the following: sodium, potassium, calcium and magnesium; total nitrogen and coagulable protein; dialysable nitrogen and amino-acids; the protein precipitation of extracts in various concentration by a variety of precipitants, and the colloid protective action for gold and mastic sol. The content of dialysable nitrogen and amino-acids was increased; this is interpreted as indicative of a qualitative change, rather than a merely quantitative one, in the protein of the cell. An increase of the monovalent ions over the bivalent ions in the ratio Na + K.: Ca. + Mg. is held to explain the swelling of the cells. Changes in the protein precipitation and colloid protective curves of the hydrophil sols of the extracts are evidence of changes in the nature of protein of the cells and its derivatives.

O. T. SCHULTZ.

NATURAL MELANINS. HEINRICH WAELSCH, Ztschr. f. physiol. Chem. **213**:35, 1932.

The melanin of the choroid and fuscin of horse's eyes and human melanin in the liver from metastatic malignant melanomas of the eye, which are characterized by a positive Tormaehlen reaction in the urine, were investigated. Choroidal melanin contains traces of iron; the other melanins are free from it. All melanins contain sulphur in considerable quantities. The chromophoric groups of the sarcoma melanins have the same elementary composition. The choroidal melanins and fuscins have different chromophoric groups and differ in this respect also from each other. The melanins contain a protein substance which cannot be digested and which can be isolated by prolonged hydrolysis by hydrochloric acid.

WILHELM C. HUEPER.

## Microbiology and Parasitology

CYSTS OF THE DYSENTERY-PRODUCING ENDAMOEBA HISTOLYTICA IN A BALTIMORE DOG. JUSTIN ANDREWS, Am. J. Trop. Med. **12**:401, 1932.

A case of natural chronic amebic infection in a Baltimore dog, in the dejecta of which cysts were found, is recorded. From the evidence, it seems strongly probable that the organism involved was Endamoeba histolytica, and that the dog may be in nature an occasional carrier of this parasite, constituting, in this condition, a reservoir of amebiasis for man and dogs.

AUTHOR'S SUMMARY.

TYPES OF TUBERCLE BACILLI ISOLATED FROM HUMAN LESIONS. R. M. PRICE, Am. Rev. Tuberc. **25**:383, 1932.

Bovine tuberculosis is an almost negligible factor in the tuberculosis of human adults. The bovine tubercle bacillus is a factor of considerable importance in the tuberculosis of childhood (in Canada); 13.6 per cent of nonpulmonary tuberculosis, leading to disablement, operation and the necessitation of prolonged and costly treatment, with doubtful results at the outcome, is caused by the bovine tubercle bacillus. The disease is milk-borne and is preventable by effective pasteurization of milk. In Toronto, where pasteurization has been compulsory since 1915, not a single case of bovine infection has been encountered (1915-1930).

H. J. CORPER.

A COMPARISON OF TISSUE REACTIONS TO TESTICULAR INOCULATION OF ACID-FAST BACILLI. ESMOND R. LONG and ARTHUR J. VORWALD, Am. Rev. Tuberc. **25**:614, 1932.

A wide range of virulence for the guinea-pig was disclosed among the acid-fast bacilli—human (H 37), bovine (Vallee, 1920), avian (Van Es, 1921) frog bacillus (M. ranae) (Moeller, 1900), timothy grass (Mycobacterium phlei) (Moeller, 1904)—injected into the testes of guinea-pigs. These strains were previously used for chemical study by other investigators. Little difference was to be seen in the effects of the human and bovine types used as 0.1 mg. in 0.3 cc. The immediate reaction to these micro-organisms was more intense than that toward the less virulent strains, and the end-result was extensive necrosis with suppuration. The gross and microscopic pictures as early as six hours after inoculation forecast with considerable accuracy the outcome at four weeks. The strain of avian bacillus used possessed unmistakable virulence, although of much lower degree than that of the human and bovine types. The lesions produced by the frog bacillus also appeared to have a progressive tendency for a time. At two weeks, although not at four, the cellular reaction was still increasing, and at that time was much more intense than that produced by the saprophytic smegma and timothy bacilli. Moreover, while no caseation necrosis developed, the inflammatory reaction was of sufficient intensity to cause profound atrophy of the seminiferous tubules. To smegma and timothy bacilli, the reaction diminished from the third day on, and necrosis did not develop. If both testes were inoculated, the one with the human bacilli and the other with smegma bacilli, there appeared to be an initial difference in the gross reaction to the tubercle bacilli. Hyperemia was absent during six to twenty-four hours, but the ultimate effect of the tubercle bacilli in the presence of the small dose (0.1 mg.) of smegma bacilli in the opposite testis was unchanged, extensive tuberculous damage with the usual suppuration resulting. On the other hand, the presence of progressive tuberculosis seemed to make the tissues less tolerant to the smegma bacillus.

H. J. CORPER.

EXPERIMENTAL TUBERCULOSIS IN THE ALBINO RAT. M. MAXIM STEINBACH, Am. Rev. Tuberc. **26**:52, 1932.

The normal rat is highly refractory to infection with the human and the bovine tubercle bacilli. Age is not a factor in this immunity. The normal rat is but slightly susceptible to intraperitoneal injection of large doses of avian bacilli. Avitaminosis decreases the resistance of the albino rat to the avian tubercle bacilli, but not to the mammalian types. Suprarenalectomy decreases the resistance of the rat to both avian and bovine tubercle bacilli, but does not affect the animal's resistance to human bacilli. Parathyroidectomy is a factor in lowering the resistance to the bovine but not to the human strain. Thyroid-parathyroidectomy renders the rat susceptible to infection with the human as well as with the bovine type of bacilli. Macroscopic and microscopic tuberculosis in the rat does not differ from that seen in other experimental animals, or in man. Pseudotuberculosis, frequent in the normal rat, can be readily differentiated histologically from true tuberculosis.

H. J. CORPER.

THE CALCIFICATION OF EXPERIMENTAL INTRAABDOMINAL TUBERCULOSIS. TOM DOUGLAS SPIES and W. REECE BERRYHILL, Am. Rev. Tuberc. **26**:275, 1932.

The administration of repeated large doses of viosterol to guinea-pigs following intraperitoneal inoculation of tubercle bacilli caused calcification of many tubercles. The calcium was deposited in the renal tissues of the tuberculous animals to a much more marked degree than in the kidneys of normal animals receiving still larger doses of viosterol. This suggests that there may be some underlying factor which is related to the tuberculous process and which affects calcium metabolism. It is suggested that a diet high in vitamin D might be beneficial in intraperitoneal tuberculosis.

H. J. CORPER.

BACILLEMIA IN TUBERCULOSIS. LITA SHAPIRO, Am. Rev. Tuberc. **26**:418, 1932.

In 167 cases of tuberculosis tested with the Löwenstein technic there were only 7 positive blood cultures (4.2 per cent). None of the 28 cases of rheumatic fever and chorea gave positive blood cultures.

H. J. CORPER.

TUBERCULOSIS IN THE INDIAN. HERBERT A. BURNS, Am. Rev. Tuberc. **26**:498, 1932.

The Indian has a death rate from tuberculosis ten times greater than his white neighbor. Racial mixing has not seemed to reduce the rate of infection with tuberculosis or the mortality from it in the Indian population. The rate of infection is much higher among the Indian than the white school children living in the same county. There are no marked differences in the clinical types occurring among the various degrees of mixed bloods, full bloods and the whites. The opportunity for contact over a long time seems to be the most important element explaining the prevalence of, and the high death rate from, tuberculosis. Tuberculosis in the Indian does not differ in any important essential from other communicable diseases. The Indian constitutes an important reservoir of infection which must be controlled to prevent the spread of the disease to the non-Indian population.

H. J. CORPER.

BLENNORRHAGIC KERATOSIS. STANLEY O. CHAMBERS and GEORGE F. KOETTER, Arch. Dermat. & Syph. **27**:411, 1933.

A case of blennorrhagic keratosis is reported, with multiple biopsies. The earliest cutaneous lesion was a minute dull red papule which became pustular in its center. A crust developed at the center of the pustule, spreading peripherally until the entire lesion was crusted. The periphery of the lesion remained pustular. Gray flat papules were present over the hard palate, the sides of the tongue and the buccal mucous membrane. Microscopic examination showed the earliest change in the superficial dermis in the form of a perivascular lymphocytic infiltration. The epidermis was involved secondarily, first with a marked edema and later with invasion of the epidermis by leukocytes. This was followed by focal necrosis in the superficial epidermis, which extended peripherally. Superficial crusting occurred, which became more and more extensive until, when activity had ceased, the entire superficial epidermis was replaced by a crust which ultimately separated, leaving smooth, hyperpigmented skin. During one exacerbation of clinical symptoms the patient had severe iritis and conjunctivitis of the left eye. This was followed by marked edema of the retina, and the entire process cleared up in about four weeks, with deposits of pigment on the anterior capsule of the lens. The complement-fixation test for gonorrhea was strongly positive. Efforts to identify the gonococcus from cultures and smears from the blood gave negative results. Aspirated material from lesions in all stages of development failed to show the gonococcus. Emulsified tissue, when placed on culture mediums, did not show the gonococcus. Attempts to bring about the development of new lesions by autoinoculation were unsuccessful.

S. W. BECKER.

STUDIES IN EXPERIMENTAL SYPHILIS. A. M. CHESNEY, T. B. TURNER and F. H. GRAUER, Bull. John Hopkins Hosp. **52**:145, 1933.

Rabbits infected with one strain of Spirochaeta pallida (Nichols strain) and treated comparatively late in the course of their disease, i. e., from six to eight and two-thirds months after the first inoculation, were subsequently inoculated with a different strain of Spirochaeta pallida (strain F) by depositing the virus on the intact genital mucous membrane. Under these conditions, 46 per cent of the test animals were successfully infected a second time. In an equal number of control normal animals inoculated in a similar manner, the incidence of positive inoculations was 62 per cent. The conclusion is drawn that the immunity which develops in rabbits during the course of a syphilitic infection is strain-specific even when tested as outlined, that is to say, in a manner which favors the host rather than the inciting agent. The occurrence of syphilitic reinfection in man and its bearing on the reported experiments with rabbits are discussed.

AUTHORS' SUMMARY.

VARIANTS OF A STRAIN OF BACILLUS DYSENTERIAE. A. COMPTON, J. Infect. Dis. **51**:428, 1932.

Two naturally occurring variants, opaque (O) and translucent (T), of an organism of the Gay-Harris group of B. dysenteriae, met with in cases of acute bacillary dysentery at Alexandria, are described. Sharply defined differences between the variants in cultural, morphologic, serologic and lytic properties are recorded, with less sharply defined differences in virulence, immunizing power and susceptibility to the bactericidal action of normal serum. There appears to be no detectable difference between them in sensitiveness to salt or in biochemical properties. Characteristic lenticular or fusiform bodies, which are a feature of colonies of the O variant on agar, are discussed. They are thought to be of the nature of bacterial aggregates, and may be a cause of the fluorescence. The usual confirmatory tests for "smoothness" and "roughness" of bacterial variants — sensitiveness to salt, clouding of broth and specific agglutination — find no application as distinguishing tests of "opaqueness" and "translucency." Instead, the differential confirmatory tests for this type of bacterial variation, as based on the present study, are internal lenticular bodies in the colony structure, fluorescence by obliquely transmitted artificial light and phage action.

AUTHOR'S SUMMARY.

ACIDURIC AND ACIDOGENIC MICRO-ORGANISM IN DENTAL CARIES. W. H. TUCKER, J. Infect. Dis. **51**:444, 1932.

Cultures prepared in acid broth ($p_H$ 5) from scrapings of the surfaces of the teeth of 422 children yielded micro-organisms of some type in practically every case. Streptococci of various types were isolated most frequently, but Lactobacillus acidophilus, Staphylococcus albus and yeasts also developed in the acid medium. An attempt was made to correlate the incidence of dental caries with the occurrence of some one type of aciduric micro-organism. This attempt was unsuccessful. Aciduric streptococci were found in the mouths of practically all of the children irrespective of the incidence of dental caries and irrespective of the ingestion of citrus fruit juice. L. acidophilus was found most frequently and most consistently in the mouths of children whose teeth contained three or more cavities. Some relationship appears, therefore, to exist between the persistent presence of L. acidophilus and cavities in the teeth. This micro-organism was not, however, always found, even in those cases in which there was shown a high susceptibility to dental caries. If one is to conclude that L. acidophilus is the cause of dental caries, one must always find this organism associated with dental caries. This I was unable to do. L. acidophilus occurred rather frequently and consistently in the mouths of children who had never had any dental caries, or who had developed no new carious lesions for two years. From this it appears that L. acidophilus is not an obligate producer of dental caries.

AUTHOR'S SUMMARY.

EFFECT OF VITAMINS A AND D IN INFECTION BY SALMONELLA ENTERITIDIS. L. S. McCLUNG and J. C. WINTERS, J. Infect. Dis. **51**:469 and 475, 1932.

A marked increase in susceptibility to infection with Salmonella enteritidis injected intraperitoneally was shown in a group of white rats fed on a vitamin A-free diet for a period of seven weeks, as compared with a control group similarly infected. A slight increase in susceptibility to infection by intraperitoneal injection of S. enteritidis was shown by a group of white rats kept for a period of seven weeks on a diet low in vitamin D, as compared with a similar group of controls kept during the same period on an adequate diet and similarly infected. This decrease in resistance to infection is not as great as that previously shown to be brought about by a deficiency of vitamin A in the diet.

AUTHORS' SUMMARIES.

ADENOTONSILLECTOMY AND COMMON COLD IN ADULTS. W. M. GAFAFER, J. Infect. Dis. **51**:489, 1932.

A group of 179 adults was observed for thirty-five weeks from Sept. 29, 1929, to May 31, 1930, and every effort was made to secure reports of all attacks of disease of the upper respiratory tract (common cold). Of these adults, 123 showed tonsils and adenoids, and 56 did not. The group with tonsils and adenoids and the group without tonsils and adenoids presented no significant difference with respect to frequency, severity or type of attack of disease of the upper respiratory tract (common cold).

AUTHOR'S SUMMARY.

## Immunology

THE ARTHUS PHENOMENON. I. HARRISON TUMPEER and E. J. COPE, Am. J. Dis. Child. **45**:343, 1933.

In a syphilitic patient with the Arthus phenomenon resulting from injections of horse serum (diphtheria antitoxin and toxin-antitoxin), precipitins to horse serum were demonstrated. The patient's serum contained a transferable substance which was toxic for rabbit and guinea-pig skin. This substance interacted with horse serum (diphtheria antitoxin) when passively transferred to a rabbit or a guinea-pig. It was capable of further demonstration by the technic of Shwartzman. The serum of the patient probably contained a transferable substance which produced a toxic interaction with donor serum in the skin of the rabbit. Controls with essentially similar serums from members of the same family similarly treated but not manifesting the Arthus picture were negative. The fatal reaction to transfusion, despite agglutinin and hemolysin compatibility, was due to other changes in the patient's blood incident to the Arthus phenomenon.

AUTHORS' SUMMARY.

THE NEUTRALIZATION OF POLIOMYELITIS VIRUS BY THE SERUM OF LIBERIAN NEGROES. N. P. HUDSON and E. H. LENNETTE, Am. J. Hyg. **17**:581, 1933.

The experimental finding that eighteen of the nineteen samples of serum from Liberian Negroes had a virucidal capacity is comparable with the results of similar analyses in the United States. We cannot ascertain what the incidence of this disease is among the Negro tribes from which the persons came who furnished the serum. Some observers report probable cases among the Liberian natives, and the acute form of the disease is recorded in other parts of tropical West Africa. On the basis of the situation in the United States, it appears that the results are compatible with a wide distribution of the poliomyelitis virus. The proper interpretation of the experimental findings depends on the significance of the neutralization test as a specific immune reaction. We failed in our attempt to find in a Negro population little exposed to whites of the temperate zone a group of persons giving negative neutralization tests, which might act as a control in analyses of

human serum elsewhere. We may conclude that the problem of the interpretation of the virucidal property of normal adult serum of Liberian Negroes is the same as in the temperate zone.

AUTHORS' SUMMARY.

THE SENSITIZATION OF GUINEA PIGS AND THE PRODUCTION OF ALLERGY AND ANAPHYLAXIS TO TUBERCULOPROTEIN. H. S. REICHLE and HARRY GOLDBLATT, Am. Rev. Tuberc. **27**:291, 1933.

Normal guinea-pigs received intracutaneous injections of from 1 to 10 per cent solutions of old tuberculin and various adjuvant substances, such as eye fluid of normal guinea-pigs and horse serum. When these animals were retested with old tuberculin within from three to eight days after the sensitizing injection, they responded in a fashion typical of bacterial allergy; 55 of 102 animals showed this phenomenon. The cutaneous reactions were of the prolonged, allergic type, and although vesiculation and ulceration were never seen, they were otherwise analogous to those observed in tuberculous animals. The same reaction was obtained with Seibert's pure tuberculoprotein. At an early stage of an experiment the animals were not sensitive to glycerin broth, but after repeated injections with old tuberculin sensitivity to glycerin broth developed. In some of the animals a positive Long testicular test for allergy to tuberculin was obtained; in others a strong anaphylactic sensitivity to tuberculin was demonstrated by means of the Dale test. It is probable than an adjuvant substance is not a necessary factor and that the essential element in all previous reports of unsuccessful artificial sensitization to tuberculin has been the tuberculin itself. Other investigators may not have been able to substantiate earlier observations because of the failure to recognize the incubation period, the use of animals weighing less than 500 Gm., which are not easily sensitized, and the lack, at that time, of an objective measure of allergy, such as the Long testicular test.

H. J. CORPER.

THE EFFECT OF TUBERCULIN ON SPERMATOZOA FROM NORMAL AND TUBERCULOUS GUINEA PIGS. LILIAN C. DONALDSON and ARTHUR J. VORWALD, Am. Rev. Tuberc. **27**:401, 1933.

By the motility test spermatozoa from tuberculous animals could not be shown to be hypersensitive to strong concentrations of tuberculin or to purified tuberculin-protein fractions. The method, therefore, is not a suitable one for testing the potency of tuberculins. Spermatozoa from tuberculous animals are apt to be slightly less motile and to sustain their motility less well in Locke's solution than spermatozoa from noninfected animals. Strong concentrations of synthetic-medium tuberculin caused an initial acceleration of motility in spermatozoa from normal and tuberculous animals. A like acceleration is caused by similar concentrations of Long's synthetic medium alone. Strong concentrations of tuberculin cause a rapid decrease in the motility of spermatozoa from both normal and tuberculous animals; a similar but less rapid decrease is caused by equal concentrations of a synthetic medium. A carbohydrate fraction derived from tuberculin and a timothy-bacillus protein likewise lessened motility rapidly. Diphtheria toxin shows no effect on the motility of spermatozoa from either tuberculous or nontuberculous animals, other than an acceleration when very strong concentrations are used.

H. J. CORPER.

IMMUNE REACTIONS IN DIABETES. JOHANNES K. MOEN and HOBART A. REIMANN, Arch. Int. Med. **51**:789, 1933.

The development of agglutinins for typhoid bacilli after the vaccination of diabetic patients and normal persons was observed. In well patients with controlled diabetes, agglutinins developed in titers similar to those in normal persons used as controls. In patients with diabetes that was controlled with more difficulty, the agglutinin response was distinctly weaker. In patients with uncontrolled diabetes

with acidosis, the agglutinin response was poor; in a few cases no agglutinin for certain strains appeared. The coincidence of the increased susceptibility of severely ill diabetic patients and the deficiency of demonstrable antibodies suggests a causal relationship of the latter to the former condition. AUTHORS' SUMMARY.

ACQUIRED IMMUNITY BY RABBITS TO SYPHILIS IS NOT DEPENDENT UPON ALLERGIC INFLAMMATION. A. R. RICH, A. M. CHESNEY and T. B. TURNER, Bull. Johns Hopkins Hosp. **52**:179, 1933.

Rabbits rendered immune to syphilis by inoculation with Spirochaeta pallida showed no allergic reaction whatever, whether macroscopically or microscopically, on intracutaneous reinoculation at periods ranging from twenty-eight to four hundred and eighty-two days after the primary, immunizing infection. On the contrary, the most striking phenomenon observed in the immune animals, as contrasted with the nonimmune controls, was always a remarkable indifference of the tissues of the former to the presence of the injected virus. Although it is well known that allergy to Spirochaeta pallida appears during human syphilitic infection and can also be induced in the rabbit, according to Noguchi, the present experiments demonstrate that allergic inflammation is not necessary for the operation of acquired immunity in syphilis. AUTHORS' SUMMARY.

THE PREVENTION OF SPREAD OF BACTERIA IN THE IMMUNE BODY. A. R. RICH, Bull. Johns Hopkins Hosp. **52**:203, 1933.

In the nonimmune body pneumococci drift freely through the tissues from the site where they are deposited and readily invade the blood stream. In the actively or passively immunized body the bacteria are held sharply at the immediate site where they lodge. The local lesion in the immune body is therefore limited in size, and septicemia, with the attendant opportunity for metastatic infection, does not occur. The immediate local immobilization of the bacteria in the immune body is accomplished by the specific action of the immune antibody which, through its effect on the bacteria, causes them to remain fixed to the tissues at the site where they lodge until they can be surrounded and destroyed by the leukocytes. In this action the immune antibody performs an important and hitherto undemonstrated protective function. The process of immediate fixation of bacteria in the immune body occurs independently of inflammation and is in operation before any effective amount of inflammation is established at the site. Inflammation, when finally established, is, of course, of great importance in contributing to the localization of the infection and in effecting the destruction of the bacteria, but it is shown that the accelerated and exaggerated inflammation of allergy is not required for the successful performance of either of these two protective functions.

AUTHOR'S SUMMARY.

STUDIES ON THE PRECIPITIN REACTION. M. HEIDELBERGER and F. E. KENDALL, J. Exper. Med. **57**:373, 1933.

The products of partial hydrolysis of the specific polysaccharide of type III pneumococcus ranging from 550 to 1,800 in formula weight can be quantitatively freed from unhydrolyzed polysaccharide. The fractions yield specific precipitates with type III antipneumococcus horse serum but fail to precipitate homologous rabbit antiserums, giving rise only to specific inhibition. The aldobionic acid, the structural unit of S, does not precipitate antiserums. A possible explanation and a possible application of the findings are pointed out.

AUTHORS' SUMMARY.

ACTIVE IMMUNIZATION AGAINST TYPHUS FEVER. H. ZINSSER and M. RUIS CASTANEDA, J. Exper. Med. **57**:381 and 391, 1933.

Vaccines consisting of formaldehydized Rickettsiae of Mexican typhus fever, obtained by our x-ray rat method, produce definite resistance in guinea-pigs to

subsequent infection with the virus of this disease. The resistance so produced amounts to complete immunity when the subsequent infectious dose is moderate, that is, when it consists of typhus blood or of tunica material in reasonable amounts (not more than one fourth of a tunica, i. e., roughly, from 100 to 250 infectious doses). When, as in the first experiment, excessive doses of infectious material were given, the vaccination protection was incomplete in two of the three animals. Subcutaneous vaccination is fully as effective as intraperitoneal, even when the subsequent infection is intraperitoneal. As in previously reported experiments, the vaccines made with the Mexican organisms conferred only partial and feeble protection against the European virus (Breinl strain). The injection of a horse with formaldehyde-killed and phenol-killed Rickettsiae from the Mexican virus induced the development of distinctive protective properties against the virus in the serum of the horse.

FROM AUTHORS' SUMMARIES.

NORMAL AND IMMUNE OPSONIN. H. K. WARD and J. F. ENDERS, J. Exper. Med. **57**:527, 1933.

In normal unheated human serum, virulent pneumococci may be prepared for phagocytosis by two separate antibodies acting in conjunction with the complement. One of these is the type-specific anticarbohydrate antibody reacting with the carbohydrate fraction of the pneumococcus. The other is probably also a type-specific antibody, but quite distinct from the former, and therefore must react with a different antigenic constituent of the bacterium. In the normal human serum heated to 56 C., these two antibodies may, after prolonged contact with the organism, promote phagocytosis of the pneumococcus without the adjuvant action of the complement. Although these two antibodies are equally effective in the phagocytosis by normal blood of organisms cultured for twenty-four hours, the anticarbohydrate antibody tends to become the predominant factor as the pneumococci approach the state in which they exist in the animal body. So far as we have been able to show, the anticarbohydrate antibody is the only antibody in immune serum which can induce phagocytosis. This substance by itself is active in a phagocytic system, but, just as in the normal serum, the complement enhances its effect. The failure to demonstrate the presence in the immune serum of an antibody distinct from the anticarbohydrate antibody and analogous to that found in the normal serum may be due to the experimental difficulty of removing all the anticarbohydrate antibody from a concentrated immune serum. Thus it is seen that a single well defined antibody (the anticarbohydrate antibody) may be responsible for the phagocytic action of normal unheated serum, normal heated serum, inactivated immune serum and immune serum activated by the complement. These facts appear to us to invalidate Neufeld's division of the phagocytic antibodies into bacteriotropins (antibodies, the phagocytic titer of which is not raised by the addition of the complement) and opsonic antibodies (antibodies comparable to the lysins, which are active only in the presence of the complement). The complement alone is incapable of inducing phagocytosis of the pneumococcus. In the phagocytic process, it appears simply to increase the speed at which the reaction takes place. Its rôle may be compared to that of a catalyst in a chemical reaction. On the basis of these findings, it is proposed that the term "tropin" be discarded as misleading and unnecessary, and that the term "opsonin" be retained to denote any heat-stable antibody which prepares bacteria for phagocytosis. Contrary to current usage, it would not suggest a combination of antibody with complement.

AUTHORS' SUMMARY.

A SEROLOGICAL DIFFERENTIATION OF HEMOLYTIC STREPTOCOCCI. R. C. LANCEFIELD, J. Exper. Med. **57**:571, 1933.

All except 2 of 106 strains of hemolytic streptococci isolated from man and other animals and from milk and cheese have been classified into 5 groups, which bear a definite relationship to the sources of the cultures. These broad groups

may be subdivided into specific types by methods discussed elsewhere. Classification in specific groups is made possible by employing two special reagents: extracts prepared by the treatment of the bacteria with hot hydrochloric acid, and serum of animals immunized with formaldehydized cultures. This differentiation is not detected by the agglutination reaction. The grouping agrees with that described by other investigators on the basis of cultural and biochemical characteristics. The group-specific substance present in strains of group A has been identified chemically as carbohydrate in nature. The chemical composition of the specific substances on which the specificity of the other groups depends has not been determined. It seems not unlikely, however, that all of them may belong in the general class of carbohydrates, each being chemically distinct and serologically specific in the individual groups.

AUTHOR'S SUMMARY.

SKIN TEST IN SERUM TREATMENT OF TYPE I PNEUMONIA. T. FRANCIS, JR., J. Exper. Med. **57**:617, 1933.

Tests of the skin were made with type I SSS in fifty-three cases of type I pneumococcus lobar pneumonia, in forty-eight of which the patients were treated with antipneumococcus type I serum. In all but one of the forty-six patients who recovered a positive, immediate reaction of the skin was obtained at about the time of recovery. In seven fatal cases the reactions were consistently negative, even in the presence of circulating type-specific antibodies. The cutaneous test has proved to be an extremely valuable guide to serum therapy, and a definite prognostic aid. It has distinct advantages over the agglutination reaction in that it is not merely an index of circulating antibodies. When positive, it invariably denotes that recovery has begun; when negative, it indicates further serum therapy. The mechanism of the positive skin test is closely related to that operative in recovery from pneumonia, and is apparently the resultant of antibody and tissue activity.

AUTHOR'S SUMMARY.

ANAPHYLACTIC SHOCK BY AZODYES. K. LANDSTEINER and J. VAN DER SCHEER, J. Exper. Med. **57**:633, 1933.

Experiments are described which show that anaphylactic shock can be induced in animals sensitized with azoproteins by injecting them with azodyes containing the same azo components as the sensitizing antigen. The anaphylactic reactions are specific and occur with quantities of the dyes as small as fractions of milligrams.

AUTHORS' SUMMARY.

CHANGES IN BACTERIAL VOLUME AS THE RESULT OF SPECIFIC AGGLUTINATION. F. S. JONES and R. B. LITTLE, J. Exper. Med. **57**:721 and 729, 1933.

Measurements indicate that bacterial antigens increase in volume as the result of specific agglutination. There is a general parallelism between the increase in antigenic volume and the concentration of the immune serum. The phenomenon is specific. There is no increase with normal serum; with absorbed serum the increase is slight and can be correlated with the presence of unabsorbed antibody. The effect is enduring, as shown by volumetric determinations on repeatedly washed, agglutinated bacteria.

When the increase in volume approximated 20 per cent, all the bacteria were agglutinated. We have attempted to correlate the volumetric increase with the quantity of protein absorbed by the organism during agglutination and have studied not only bacteria but also collodion particles first sensitized to antigen and then agglutinated with a precipitin specific for the antigen. The increase in volume of the collodion particles was small, and the quantity of protein adsorbed was relatively large. When two species of bacteria were agglutinated with their respective antiserums the reverse was true; the apparent increase in volume was

much greater than the quantity of protein deposited during the reaction. There is, then, no direct correlation between the deposition of protein and the apparent increase in volume. Nevertheless, the results of the experiments here reported have suggested an explanation for the increase in volume.

AUTHORS' SUMMARIES.

INHERITED AND ACQUIRED FACTORS IN RESISTANCE TO INFECTION. L. T. WEBSTER, J. Exper. Med. **57**:793 and 819, 1933.

The experiments are a step in the analysis of inherent resistance to infection. Heredity has proved clearly to be an element of fundamental importance in determining the fate of individuals following primary exposure to a natural infection. Innate susceptibility or resistance factors in the genetic sense were not sex-linked or related to body vigor, as expressed by unusual fertility or weight. Indeed, so far as these experiments are concerned, all lines of mice tested, save possibly the white-face, were sturdy and normal. The genetic factors are probably multiple, with resistance dominant to susceptibility. Again, the tissues of susceptible mice, not only at the surface but throughout the body, appeared to be more sensitive to Bacillus enteritidis than did those of resistant mice, suggesting the general rather than local influence of the inherent factors. Finally, the facts that the white-face line proved relatively susceptible to enteric, respiratory and virus infections, that the Rockefeller Institute susceptible lines were relatively susceptible to enteric and respiratory infections but were resistant to virus infections, and that the Rockefeller Institute resistant lines were resistant to enteric and respiratory infections but were susceptible to virus infections, together with previous observations, indicate that genetic factors segregated by selective and brother-sister inbreeding and concerned with susceptibility or resistance to infection can operate consistently against a number of, but not necessarily all, harmful agents.

AUTHOR'S SUMMARIES.

PHENOMENON OF LOCAL SKIN REACTIVITY TO BACTERIAL FILTRATES IN ITS RELATION TO BACTERIAL HYPERSENSITIVENESS. G. SHWARTZMAN, J. Exper. Med. **57**:859, 1933.

The observations reported in this article demonstrate that the intravascular interaction of bacterial and animal protein antigens with homologous antibodies at the site of a tissue made vulnerable by bacterial filtrates induces prompt severe hemorrhagic necrosis in this tissue. In the light of these observations an explanation of the mechanism underlying focal and cutaneous bacterial hypersensitiveness is offered.

AUTHOR'S SUMMARY.

THE IMMUNOLOGICAL RELATION OF POLIOMYELITIS TO LOUPING ILL. F. F. SCHWENTKER, T. M. RIVERS and M. H. FINKELSTEIN, J. Exper. Med. **57**: 955, 1933.

The results of the work presented in the present paper show that louping ill and poliomyelitis are not closely related immunologically. Although relatively few experiments were performed, the data obtained were sufficiently decisive for our purposes. Certainly nothing was found to indicate that one might be able to immunize human beings against poliomyelitis by the use of the virus of louping ill. In addition to the negative findings, a certain amount of useful information was also secured, namely: Monkeys can be solidly immunized against louping ill by intraperitoneal injections of virus and partially protected by intramuscular administrations of the active agent; during the process of immunization, no signs of involvement of the central nervous system are manifested, and serums from monkeys immunized in the manner described contain antibodies capable of neutralizing the virus.

AUTHORS' SUMMARY.

H AND O TYPHOID AGGLUTINATION. A. D. DULANEY ET AL., J. Immunol. **24**: 229 and 235, 1933.

Vaccination against typhoid stimulates the production of H agglutinins to high titers. O agglutinins are also stimulated, but show much lower titers. O agglutination in serum dilutions of 1:100 was demonstrated in 26 per cent of all vaccinated serums and in 11 per cent of a random group of persons. If O agglutination is to have diagnostic value in typhoid fever, higher dilutions of serum than those recommended by Felix (1:100) must be employed. We recommend dilutions of 1:500. In the usual course of typhoid fever both H and O agglutinins are produced. H and O agglutinins to appreciable titer (1:500) are not demonstrated in unvaccinated persons suffering from nontyphoid diseases. O agglutinins seem definitely related to infection. Their demonstration in dilutions of from 1:500 to 1:1,000 is highly suggestive of infection by a member of the typhoid-paratyphoid group, since neither vaccine nor other febrile diseases stimulate to such titers. Typhoid vaccine stimulates the production of H agglutinins to high titers and O agglutinins to low titers (from 1:40 to 1:320). The ordinary Widal test detects only H agglutinins and does not differentiate between infection and vaccination. The use of preserved formaldehydized and alcoholized antigens offers an easy and standardized method of demonstrating H and O agglutinins. H and O agglutination is recommended as a laboratory procedure in typhoid fever, though it could never have the validity of isolation of the causative organism.

AUTHORS' SUMMARIES.

THE INACTIVATION BY HUMAN SERUM OF THE VIRUS OF POLIOMYELITIS. C. W. JUNGEBLUT and E. T. ENGLE, J. Immunol. **24**:267, 1933.

The two sets of experiments, taken together, suggest that the power of normal adult human serums to inactivate the poliomyelitis virus in vitro is not a fixed property but may change appreciably in consonance with certain physiologic fluctuations in the endocrine balance of the individual. Thus it becomes increasingly difficult to harmonize the foregoing observations with the orthodox conception, which regards these virucidal substances as the specific reaction product of previous exposure to the virus.

AUTHORS' SUMMARY.

CARBOHYDRATE TYPE-SPECIFIC SUBSTANCES OF PNEUMOCOCCUS. A. WADSWORTH and R. BROWN, J. Immunol. **24**:349, 1933.

Type-specific substances of carbohydrate nature obtained from the cells of types I, II and III pneumococci and a nontype-specific substance of carbohydrate nature obtained from an attenuated type I organism were distinct among themselves and also differed from the soluble specific substances of Heidelberger, Avery and others and from the C fraction of Tillett and Francis.

AUTHORS' SUMMARY.

A METHOD FOR SECURING CLEAR SERUMS FROM THE MILK OF COWS AND GOATS. I. C. HALL and R. LEARMONTH, J. Infect. Dis. **52**:27, 1933.

In practice, test tubes for the collection of samples of milk are corked in the laboratory, each containing a few cubic centimeters of either chloroform or carbon tetrachloride and a small amount of rennet extract. They are then taken to the dairy and used for the collection of each sample directly from the animal. Each tube is then shaken thoroughly for several minutes to extract the fat. On being returned to the laboratory, all the tubes are placed in the incubator at 37 C. for about an hour to coagulate the casein. They are then centrifugated for fifteen minutes at 2,000 revolutions per minute to separate the milk serum, which will be found in a perfectly clear, deep layer at the top, with a compact curd in the center and the solvent in the bottom. Milk serums collected in this manner may be preserved indefinitely without bacterial growth, owing to the germicidal action

of the solvents, but we have not tested the stability of agglutinins under these conditions. There is no interference with the agglutination test for Bacterium melitensis either by inhibition or by false agglutination. If larger numbers of tests are made, it would probably pay to recover the solvents for repeated use by distillation. Carbon disulphide and tetrachlorethane were also tested but were found unsatisfactory, although with both the milk serum separates at the top. But both these solvents definitely inhibit agglutination in the lower dilutions. The use of chloroform or of carbon tetrachloride with rennet in securing clear milk serums from goats and cows for agglutination tests with Bact. melitensis is recommended.

FROM AUTHORS' SUMMARY.

PRODUCTION OF AN ANTIPERTUSSIS SERUM OF HIGH TITER. J. H. BAILEY, J. Infect. Dis. **52**:97, 1933.

By repeated intraperitoneal injections into cocks of massive doses of a suspension of live, virulent pertussis bacilli, an antipertussis serum of high titer was produced, which did not cause serum sickness, even in large doses and which, in the limited trial afforded it, gave evidence of being of value in the treatment of pertussis in children. No definite statement as to the therapeutic value of this serum may be made until a greater number of patients have been treated.

AUTHOR'S SUMMARY.

AN AGGLUTINATIVE CLASSIFICATION OF THE HEMOLYTIC STREPTOCOCCUS OF SCARLET FEVER. H. J. MUELLER and K. S. KLISE, J. Infect. Dis. **52**:139, 1933.

Two hundred and twenty-five strains of hemolytic streptococci from patients with scarlet fever have been examined by agglutination. Two thirds of these fall into six well defined groups; the others remain unclassified. These types include four Griffith types, three of the five Williams types and two groups not included by these workers. These groups are seldom found in normal throats without relation to streptococcic disease. There is evidence that agglutinability is a reasonably constant attribute of hemolytic streptococci, as of other organisms. An agglutinative study of patients with scarlet fever and carriers in isolated epidemics of scarlet fever should be of material assistance in their control.

AUTHORS' SUMMARY.

## Tumors

CYTOLOGICAL CHANGES AFTER IRRADIATION OF MALIGNANT GROWTHS. R. J. LUDFORD, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 125.

*Cytology of the Transplantable Mammary Carcinoma 27 and the Changes Induced by Irradiation.*—A typical cell of this tumor contains a nucleus with one or more plasmosomes and scattered granules of chromatin. In the cytoplasm are filamentous granular mitochondria and Golgi bodies usually grouped together at the side of the nucleus. Secretion is formed in relationship with the Golgi bodies. In the course of degeneration the nucleus shrinks, the chromatin granules run together, and pyknotic nuclei result; the mitochondria break up into granules which become vesicular, and the Golgi bodies disintegrate. The cytologic changes observed after irradiation are as follows: an immediate action on the mitochondria, which become vesicular (forty minutes); inhibition of mitosis (four and one-half hours); growth in the size of the cells, accompanied by an increase in the number of the mitochondria, and enlargement of the Golgi apparatus (twenty-four hours); a return of mitosis, and an indication of intense secretory activity. Considerably enlarged cells are found as late as fourteen days after irradiation, but after three days degenerative changes occur in the enlarged cells to an increasing extent. During degeneration of the large cells the chromatin granules tend to run together

and become converted into an achromatinic substance, and the mitochondria become vesicular and finally fail to stain, while the Golgi bodies are broken up.

*Cytology of the Transplantable Mammary Carcinoma 63 and the Changes Induced by Irradiation.*—This tumor grows more rapidly than tumor 27, and its cells exhibit no indication of secretory activity. Irradiation results in inhibition of mitosis followed by an outburst of mitotic activity marked by various abnormalities. Enlargement of the cells occurs, but to nothing like the same extent as in tumor 27. The enlarged cells do not secrete, but undergo degeneration. The mitochondria become swollen and vesicular. The Golgi bodies are broken up. These disintegrating cytoplasmic organs are scattered in the cytoplasm.

*Cytology of the Transplantable Sarcoma 37 and the Changes Induced by Irradiation.*—A typical cell of this tumor has a nucleus with one or more large plasmosomes and scattered granules of chromatin. Its mitochondria are filamentous and granular and tend to collect around the sphere, which is surrounded by a compact group of Golgi bodies. During degeneration the nuclei usually become shrunken and pyknotic, the mitochondria vesicular and the Golgi bodies fragmented. The cytologic changes observed after irradiation are similar to those in tumor 63. There are the same inhibition of mitosis, much the same degree of enlargement and wave of abnormal mitoses and then progressive degeneration. Enlargement of the cells is accompanied by an increase in the number of mitochondria and an enlargement of the Golgi apparatus. During degeneration the disintegrating cytoplasmic organs tend to be collected around the sphere.

*Influence of Irradiation on the Reaction of Cells to the Vital Dye Trypan Blue.*—There is an increased staining of both normal and malignant cells morphologically altered by irradiation. Irradiated tumor cells do not stain in the same way as their nonmalignant prototypes, nor can segregation of dye be demonstrated immediately after irradiation. Not all strains of transplantable tumor exhibit staining of the enlarged cells following treatment with radium.

*Immediate and Late Effects of Irradiation on Different Types of Cells.*—The primary effects of irradiation on the colloidal state of protoplasm are probably the same in all cells, as well as the concomitant inhibition of mitosis, but the capacity for recovery, as well as the later changes, differs widely with different types of cells. The greater outburst of mitotic activity after irradiation of the more rapidly growing tumors probably results in larger numbers of nonviable daughter cells, and hence greater cell destruction. Irradiation has no specific action on cancer cells as such.

*Direct and Indirect Effects of Irradiation.*—The cytologic changes described in this paper are those which occur when malignant growths are irradiated in vivo and left in situ. As Cramer (1932) has demonstrated in another paper in this report, the clinical results of irradiation are not due alone to the direct action of the rays on the malignant cells. Irradiation also induces changes in the stroma, especially in the blood vessels. Thus direct injury to the malignant cells is intensified by interference with their nutrition. The alterations in the cells are therefore the combined result of a direct and an indirect action of the irradiation on the parenchyma of the tumor.

AUTHOR'S SUMMARY.

THE DIFFERENTIAL REACTION TO TRYPAN BLUE OF NORMAL AND MALIGNANT CELLS IN VITRO. R. J. LUDFORD, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 169.

*Mouse Fibroblasts and Sarcoma Cells.*—Fibroblasts of embryonic and adult tissues, as well as those of reaction tissues, segregate trypan blue in vitro in the form of droplets. Unfavorable conditions of growth interfere with segregation. Cell death results in diffuse passive coloration. In cultures of mouse sarcomas the macrophages stain intensely, but not the malignant cells. Although these sarcoma cells do not segregate dye as do fibroblasts, staining occurs in some degenerating cells, and under unfavorable conditions of growth. Sarcoma cells,

like fibroblasts, exhibit phagocytic activity. This affords clear evidence that segregation and phagocytosis are two different processes. Dead sarcoma cells show a diffuse passive coloration.

*Mammary Gland Cells and Mammary Carcinoma Cells of the Mouse.*—Mammary gland cells are usually intensely stained in vitro. When growing as a sheet, the cells become filled with fine droplets of the dye. The carcinoma cells in cultures of tumors 27, 63 and 206 do not segregate dye, although they may exhibit considerable phagocytic activity. Vital staining with trypan blue affords a good method for distinguishing between carcinoma cells and the macrophages which wander out from explants, since the latter stain intensely and the carcinoma cells do not.

*Mouse Epidermal Cells and Carcinoma Cells of Epidermal Origin.*—In cultures of embryonic mouse skin growing as a sheet on the surface of a plasma clot the epidermal cells segregate dye as fine droplets, and occasionally come to contain large colored inclusions, probably passively colored keratohyalin. The malignant cells of the transplantable tumor 2146, which originates as a tar carcinoma, do not segregate dye, although macrophages of the same tumor stain intensely.

*Rat Fibroblasts and Sarcoma Cells.*—Rat fibroblasts segregate trypan blue in vitro in the same manner as those of the mouse. In cultures of the Jensen rat sarcoma and of sarcoma 41, the macrophage type of cell is intensely stained. The sarcoma cells sometimes segregate dye, and in some cultures of the Jensen sarcoma there has been observed a considerable amount of segregation. This has occurred when the tumor was growing badly in vivo, and it is suggested that there may be some relation between segregation and the state of activity of the cells. The cells of both the Jensen sarcoma and sarcoma 41 are actively phagocytic.

*Fibroblasts and Cells of the Filtrable Tumors of the Fowl.*—Fibroblasts in cultures of chick embryo heart react to trypan blue in the same manner as those of the mouse and rat. Macrophages which wander out from the explants in cultures of the filtrable tumors of the fowl stain intensely with trypan blue. They are not regarded as the malignant cells of these tumors. In the cultures there is another type of cell which rarely contains much dye and which is regarded as the malignant cell. Frequently these cells do not wander out from the explants, and are therefore best studied by teasing, or by cutting serial sections. The cells of the endothelioma MH2 are actively phagocytic.

Cancer cells, when growing in vitro, do not segregate trypan blue in the same way as their nonmalignant prototypes.

AUTHOR'S SUMMARY.

VITAL STAINING OF FOWL TUMOURS. L. FOULDS, Tenth Scientific Report of The Imperial Cancer Research Fund, 1932, p. 191.

It is shown that the parenchyma cells of six varieties of filtrable tumor of the fowl rarely segregate trypan blue under conditions which lead to its active segregation by histiocytes, fibroblasts and other normal cells. Under certain conditions the cells of the endothelioma Mill Hill 2 are strongly phagocytic and may ingest large amounts of granular dye. Similar activity was not observed in tumors of other types. The absence of segregation is common to all the tumors examined, and is independent of the cell type, rate of growth or degree of differentiation. The fibrosarcomas are almost benign tumors which form abundant collagen and varying amounts of elastic tissue, and allow the survival of the host for many weeks or months. At the other extreme stands the Rous sarcoma 1, which is very cellular, forms little collagen (which is prone to degeneration) and kills the fowl, usually in three weeks. There is no constant difference in staining between these strongly contrasted types. The slow growth of the fibrosarcomas allows intense staining of the fowls and, during the time required, the tumors increase little in size. Here there can be no question, as may be raised for the sarcomas, whether the administration of dye can keep pace with the increasing bulk of the tumor. The deposition of dye at the periphery of the cytoplasm and in the intercellular matrix of these growths, which I interpret as an adsorption to fibrils, demonstrates

the access of dye to the surface of cells in the densest parts of the growths, although the cells fail to segregate it. Each of the tumors contains cells with dye, usually small in amount. It is difficult to determine the exact proportion of cells which stain on account of the uncertainty in the differentiation of tumor cells from stroma cells. It is clear, however, that they form only a minority. The observations here described correspond closely to those of Ludford (1929) and others on tumors of mice and to observations on the same tumors cultivated in vitro (Ludford, 1932). In vivo and in vitro, the parenchyma cells of tumors of fowls differ from their normal prototypes in their reaction to trypan blue, but closely resemble the cells of tumors of mice. Vital staining with trypan blue, therefore, reveals no difference between avian and mammalian neoplasms. AUTHOR'S SUMMARY.

RETROPERITONEAL GANGLIONEUROMA. N. HORTOLOMEI, G. CHIPAIL and M. FERDMANN, Ann. d'anat. path. **9**:585, 1932.

A retroperitoneal ganglioneuroma is described, composed of nerve fibers and sympathetic ganglion cells. The subject is discussed, especially the work of Masson. The tumors are rare; they are benign, and they are derived from the sympathetic nervous system and its derivatives (suprarenal medulla).

PERRY J. MELNICK.

THE HISTOLOGY OF KAPOSI'S SARCOMATOSIS. H. HAMDI and HASSAN RESAT, Ann. d'anat. path. **9**:593, 1932.

The authors studied three cases of Kaposi's sarcomatosis. These multiple growths of the skin are vascular tumors with marked perivascular proliferation of cells. The early stages appear like angiofibromas. Later there is a marked increase in vascularity, the new-formed vessels varying in caliber from the diameter of a red cell to the size of an arteriole. The proliferating perivascular cells are fusiform, and in the older lesions they are markedly increased in number and are round to oval. The lymphatics are compressed and dilated. Each lesion is entirely independent of the others. The variations in the histologic picture have resulted in different opinions among various authors. PERRY J. MELNICK.

MYELOMA. N. BALAN and L. BALLIF, Ann. d'anat. path. **9**:873, 1932.

The authors give a general discussion of myeloma and present a case of plasmocytoma, which is interesting because large numbers of megakaryocytes and eosinophils were found in some of the nodes. PERRY J. MELNICK.

CONGENITAL EPULIS (ITS HISTOGENESIS). P. MOULONGUET and GENEVIEVE DELAMBERT, Ann. d'anat. path. **9**:887, 1932.

In studying thirteen cases of the rare congenital epulis, the authors came to the conclusion that it is a form of benign adamantinoma, a sort of embryonic misplacement of nests of ameloblasts. The spongy cells surrounding the nests of ameloblasts are interpreted as degenerated groups of these cells, similar to the central degenerated spongy cells of ordinary adamantinomas, but having an opposite polarity or distribution.

PERRY J. MELNICK.

ARACHNOIDAL ANGIOMAS AND TELANGIECTASIAS. L. CORNIL and H. MOSINGER, Ann. d'anat. path. **9**:955, 1932.

In a thorough review of arachnoidal telangiectasias and angiomas, the authors come to the following general conclusions: Telangiectasias (venous capillary or arterial) are of congenital or acquired origin. In the latter case, traumatic or inflammatory causes are important. In a number of cases angiomas are engrafted on preexisting telangiectasias of an inflammatory nature, i. e., a capillary proliferation of a reactive nature which becomes transformed into a hyperplastic tumor-like process.

PERRY J. MELNICK.

## Medicolegal Pathology

AN OUTBREAK OF THALLICOSIS. J. C. MUNCH, H. M. GINSBURG and C. E. NIXON, J. A. M. A. **100**:1315, 1933.

Of thirty persons who ate tortillas containing grain with about 1 per cent of thallium sulphate, symptoms of intoxication developed in twenty within from one to three days, six of whom died. The symptoms were abdominal colic, nausea, vomiting and diarrhea or constipation, stomatitis, alopecia, peripheral neuritis, strabismus and other indications of cerebral involvement. Postmortem examination showed grossly alopecia, stomatitis, yellow liver and pulmonary and leptomeningeal congestion. The microscopic examination showed fatty infiltration and central necrosis in the liver, diffuse nephritis, gastro-enteritis, degeneration and hemorrhages in the suprarenal medulla and degeneration of the nerve cells. Thallium was demonstrated in the kidneys, liver, lungs and spleen.

BLOOD GROUPING IN QUESTIONS OF BLOOD RELATIONSHIP. A. S. WIENER, J. Immunol. **24**:443, 1933.

The chances of proving nonpaternity, when the type of the falsely accused man is known, were calculated. In New York City the average chances of proving nonpaternity by means of all four agglutinogens, A, B, M and N, are approximately one in three. A man of type A + + has less than one chance in ten to prove his innocence, and a man of type B + + has only one chance in seven. Men of the remaining ten types, however, have chances ranging from one in four (O + +) up to two in three (AB — +). The chances of detecting interchange of infants in hospitals by means of the agglutinogens, A, B and M and N, are seven in ten.

AUTHOR'S SUMMARY.

EMISSION SPECTROGRAPHY IN DETECTION OF METALS IN TISSUES. W. GERLACH and K. RUTHARDT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:151, 1932.

With the spectrographic method, sensitive elements, such as gold, silver, copper, manganese, lead, thallium and mercury, can be easily demonstrated and their presence photographically recorded. The technical procedures do not require more time than a qualitative chemical analysis.

E. L. MILOSLAVICH.

THE CHARACTERISTICS OF BLOOD GROUPS M AND N. W. CROME, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:316, 1933.

Of 1,300 persons, 49 per cent belonged to group MN; 32.5 per cent to group M, and 18.5 per cent to group N. These groups act as mendelian genes as determined in a study of 22 families with 50 children. Three pairs of monozygotic twins were found to belong to the same blood group. The method requires careful controls and an experienced serologist. It is a valuable addition to our methods of studying paternity and maternity relations.

JACOB KLEIN.

THE USE OF NITRIC OXIDE GAS IN THE DIAGNOSIS OF AIR EMBOLISM AND DEMONSTRATION OF RESPIRATORY ACTIVITY IN THE NEW-BORN. DYRENFURTH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:341, 1933.

Two analytic gas methods are described for determining the presence of oxygen in the given tissues (lungs). The one consists of placing the previously dried and hardened tissue in a cylinder with a measured amount of nitrogen. The chamber is then heated, thus liberating oxygen from the tissues. This mingles with the nitrogen in the cylinder, the amount of oxygen being determined by buret titration with alkaline pyrogallic solution. The other method exposes the tissues to nitric oxide gas. This forms nitrogen dioxide with the liberated oxygen. The nitrogen dioxide is mixed with potassium iodide solution, thus liberating free iodine

which is titrated with tenth-normal thiosulphate solution, 1 cc. of which equals 1.14 cc. of oxygen. In this report there is no particular application of the method to air embolism; the emphasis is placed on the technic.

JACOB KLEIN.

STRANGULATION WITHOUT LOCAL SIGNS OF TRAUMA. (THE MEDICOLEGAL SIGNIFICANCE OF HERING'S CAROTID-SINUS REFLEX.) A. ESSER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:361, 1933.

A girl was found dead with a loop about her neck under conditions which indicated suicide. However, her lover confessed that he had choked her and then arranged the loop. The unusual feature was the lack of local changes ordinarily associated with choking. There is a detailed discussion of Hering's reflex as a cause of sudden death. It has been demonstrated experimentally by Hering that pressure on the carotid, particularly over the carotid sinus, causes a lowering of the pulse rate and blood pressure. In certain persons unconsciousness may result. This possibility should be considered in cases of death from strangulation.

JACOB KLEIN.

HISTOLOGIC STUDIES OF LUNG TISSUE IN THE NEW-BORN AS A TEST OF VIABILITY. K. BÖHMER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:391, 1933.

Tests for the demonstration of previous respiration in new-born infants are in many respects inadequate. The author studied the elastic tissue in a series of new-born infants with Weigert's stain, where the blue color is induced by the action of oxygen on the iron chloride in the stain. The author concludes that this method is an important aid in determining whether or not respiration of air has occurred in the new-born. There was a distinct difference noted in the staining of the elastic tissues in atelectatic lungs and those which had functioned. In the latter instance the oxygen in the tissues oxidizes the iron in Weigert's stain with resulting dark blue color in the elastic tissue.

JACOB KLEIN.

THE BRONCHIAL TREE IN THE DECOMPOSING LUNG OF THE NEW-BORN. A. FOERSTER, Deutsche Ztschr. f. d. gerichtl. Med. **20**:420, 1933.

The determination of the occurrence of spontaneous respiration is difficult in decomposing pulmonary tissue of the new-born. By using Weigert's elastic tissue stain the bronchial tree may be readily demonstrated, even when other tissue elements are disintegrated. On the basis of the examination of sixty lungs of new-born infants and from four medicolegal cases, the author concludes that the method satisfactorily demonstrates the bronchial tree, which is fully expanded when respiration has taken place. However, the diagnosis must not be made on one section, but should include a study of the lung from the hilus to the periphery.

JACOB KLEIN.

CHANGES IN THE RESPIRATORY ORGANS FROM SUDDEN EXPOSURE TO HIGH TEMPERATURES. A. FOERSTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:445, 1933.

Peculiar changes occurred in the bronchial mucosa in two cases in which the lungs were exposed to heat by aspiration. The epithelium of the bronchial mucosa became markedly elongated and arranged in "palisade" formation. The same changes were demonstrated in vital and postmortem experiments on dogs.

JACOB KLEIN.

SPONTANEOUS OR TRAUMATIC RUPTURE OF THE AORTA. A. ESSER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:27, 1933.

A man, while sitting on a porch, fell two stories to the ground and immediately died. There were found hemopericardium, rupture of the pericardium, arterio-

sclerosis of the coronaries and a complete tear in the aorta, 2.5 cm. below the arch. It was concluded that the site and nature of the rupture proved it to be due to trauma sustained in the fall.

JACOB KLEIN.

FAT EMBOLISM OF THE LUNGS OF A BURNT HUMAN BODY. R. KOCKEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:112, 1933.

In a burnt motor truck was found on the driver's seat a partially incinerated human body. The question arose whether this was the body of the driver. It was established that the body was that of a rather young man of slender build with reddish hair. The heart blood did not contain any carbon monoxide. There was no soot in the respiratory passages, and the lungs showed well marked fat embolism. From these observations it was concluded that the body was not that of the driver, that it had been burnt after death, and that the fat embolism in the lungs was the result of injuries received during life. The subsequent developments in the case substantiated these conclusions. The driver was found to be alive. The motive of the crime was to obtain certain insurance money.

VITAL REACTIONS OF BRONCHIAL ELASTIC FIBERS. A. FOERSTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:146, 1933.

The longitudinal elastic fibers of the bronchi were studied microscopically in animals which had been exposed to heat. The elastic fibers (Mallory stain) were markedly distorted into a characteristic network. Such changes were not seen in animals exposed to heat post mortem.

JACOB KLEIN.

INTRAVITAL ENCLOSURE OF AIR BUBBLES IN CLOTS. K. WALCHER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:146, 1933.

In a fatal case of pneumohemothorax from a bullet wound through both upper pulmonary lobes, the superior vena cava, the bronchi and descending aorta, air bubbles enclosed in fibrin were found in the blood clots. The presence of air bubbles indicates that the pneumohemothorax occurred during life.

JACOB KLEIN.

SUDDEN DEATH FROM A PEDUNCULATED LIPOMA OF THE ESOPHAGUS. G. WEYRICH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:164, 1933.

A 58 year old man, who had died suddenly without any previous illness, was found to have a pedunculated lipoma, 9.5 cm. long, attached to the anterior wall of the esophagus. The free end of the tumor had obstructed the larynx and caused death by suffocation.

JACOB KLEIN.

BLOOD GROUP DETERMINATIONS ON THE CADAVER. GEORG STRASSMANN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:168, 1933.

In the putrefying cadaver when serum is not otherwise obtainable, blood grouping may be successfully carried out on pericardial fluid, pleural and abdominal transudate, hydrocele fluid, serum from blisters on the skin, contents of the seminal vesicles, vaginal secretions and saliva.

JACOB KLEIN.

CONTRECOUP INJURIES OF THE BRAIN. E. HELLENTHAL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:250, 1933.

Contrecoup injuries result from the action of blunt force on the skull, and arise from direct extension of the impulse in the brain, with slight lateral spread. On reaching a ventricle a traumatic impulse is diffused in all directions, the lateral impulse being exaggerated. The fluid in the subarachnoid space acts as a pro-

tection to the brain. The parts of the brain most frequently involved are the lower surfaces and tip of the frontal and temporal lobes, chiefly where there is transition from the base, due to an absence of protective liquid at these places. Several traumatic impulses may arouse waves which meet at a point in the brain and cause the so-called central rupture of the brain.

JACOB KLEIN.

CHLORATE POISONING. W. BOSÆUS, Upsala läkaref. förh. **37**:341, 1932.

Two new cases of chlorate poisoning are described, one suicidal and one accidental. A fundamental difference between poisoning from sodium chlorate and that from potassium chlorate does not seem to exist. In the early stages of the poisoning, hemoglobin may be set free in the form of yellow granules; there may be signs of regeneration of red cells with erythroblasts and red cells with basophil and polychromatophil granules. At the same time, there may be leukocytosis with an increase in the percentage of polymorphonuclear nuclei and a decrease of the small lymphocytes. Fat deposits may appear in leukocytes. In the epithelial cells of the renal tubules may be found drops of hemoglobin; in a protracted case, casts of hemoglobin in the collecting tubules appeared to have set up foreign body reactions in the surrounding tissue. In two of the cases described by the author, fat embolism and extensive fat infiltration were observed in different tissues and organs. The fat embolism is regarded as the result of lipemia, because in both cases the fat drops contained lipoid substances. Pure fat emboli were scarce. In one of these cases thrombi had formed in the liver, consisting of a mixture of fat drops and blood detritus. These thrombi were found especially about small foci of necrosis due to capillary obstruction. It appears that when ulceration in the digestive tract develops in chlorate poisoning, the ulcerative lesions are of the same type as those observed in other conditions with severe blood disintegration.

FROM AUTHOR'S SUMMARY.

## Technical

IMMEDIATE TYPING OF PNEUMOCOCCI IN SPUTUM. A. R. SABIN, J. A. M. A. **100**:1584, 1933.

The method is based on the change that develops in the peripheral zones of the pneumococcus when it is placed in specific immune serum. This phenomenon was described first by Neufeld. Sabin places two small flecks of sputum on the same cover slip and covers one with immune rabbit serum, type 1, and the other with immune rabbit serum, type 2. A loopful of standard alkaline, methylthionine chloride, U. S. P. (methylene blue), is added in each case. In the type-specific mixtures the pneumococci, stained blue, are surrounded by a refractile substance resembling ground glass.

METHOD FOR MOUNTING GROSS PREPARATIONS IN A MUSEUM. S. MAHRBURG, Virchows Arch. f. path. Anat. **289**:312, 1933.

The author describes a simple and inexpensive method of mounting gross specimens on a glass plate in glycerin jelly. After the jelly has set it is rendered insoluble by treatment with solution of formaldehyde, and the reverse side of the specimen is painted with tar, obviating the use of any sort of container.

O. T. SCHULTZ.

# Society Transactions

## PATHOLOGICAL SOCIETY OF EASTERN NEW YORK

ARTHUR W. WRIGHT, *Secretary*

*Regular Meeting, Feb. 3, 1933*

STEPHEN H. CURTIS, *Presiding*

### GANGLIONEUROMA OF THE LEFT RETROPERITONEAL SYMPATHETIC CHAIN. J. SCHLEIFSTEIN.

Ganglioneuroma is still sufficiently rare to warrant the recording of new cases. This case occurred in a girl, single, 18 years of age. With the exception of the usual children's diseases and a tonsillectomy in 1930, she was healthy, doing all kinds of farm labor such as running a tractor and plowing. Three years ago, while stanchioning the cows, she was bunted in the lower middle portion of the abdomen. She was not disabled, but suffered some discomfort for a few days. In January, 1930, she hurt her back, but was not confined to bed.

About a month later she began to have pain in the lower lumbar region, which lasted for a few days. Subsequently, similar attacks occurred. At times the pain traveled down the legs, but was always present in the back and the left side of the abdomen. In the spring of 1931 she weighed 125 pounds (56.7 Kg.); on examination, 112 pounds (50.8 Kg.). Examination of the chest showed no abnormalities; the menstrual history was essentially normal, and significant neurologic symptoms were absent. No findings of diagnostic importance were obtained by laboratory tests. Physical examination showed a large mass on the left side of the abdomen in the lumbar region, which gave no pain on palpation. It did not seem to extend into the pelvis or protrude beyond the costal border, but reached to the midline of the abdomen. An operation was performed, and a large retroperitoneal tumor was found. The posterior peritoneal layer was incised, and an attempt was made to enucleate it. Since the tumor could not be defined and was firmly affixed, removal was not attempted. It extended to the pelvis and as far as the kidney, but did not include the latter. A few sections were taken for biopsy, and the abdomen was closed. The patient remained in the hospital for five days, made an uneventful recovery from the immediate operation, and was allowed to go home. The subsequent history of the case indicated that the patient was apparently in good health eighteen months after the operation.

*Histologic Examination.*—Three small sections of tissue were received, each about the size of an almond. They were grayish pink and somewhat soft.

The tumor consisted essentially of two main elements: bundles of nerve fibers, chiefly nonmedullated, and large ganglion cells. Numerous compact bundles of nerve fibers extended in various directions. Many unipolar and bipolar ganglion cells were observed which approached the form of large round cells and tended to occur in foci. Various stages of degeneration were noted in several of them. The supporting connective tissue appeared somewhat myxomatous and contained small foci of lymphocytes. The tumor was a typical ganglioneuroma, arising probably from the left retroperitoneal sympathetic chain. The kidney and suprarenal appeared to be free.

### FIBROMA OF THE UMBILICUS. J. SCHLEIFSTEIN.

A girl, 16 years of age, was thought to have an umbilical hernia. The umbilicus with the surrounding tissue was removed at operation and submitted for histologic examination.

*Histologic Examination.*—An umbilicus, quite firm, about the size of an almond and raised above the surrounding skin, was received. Cut section showed a grayish-white surface composed principally of fibrous tissue. The tumor appears to consist chiefly of fibrous connective tissue containing numerous sweat glands. The findings seem to correspond closely to those described by Cullen (Embryology, Anatomy, and Diseases of the Umbilicus Together With Diseases of the Urachus, Philadelphia, W. B. Saunders Company, 1916, p. 537) as characteristic of fibroma of the umbilicus. This specimen is of interest because of the infrequent occurrence of the condition.

SARCOMA OF THE STOMACH. J. SCHLEIFSTEIN.

Sarcoma of the stomach is still sufficiently rare to be placed on record. The patient was a married woman, 46 years of age. The only history available was that a laparotomy was done. A tumor, the size of a walnut, was found on the greater curvature of the stomach and removed. The surgeon did not consider it malignant.

*Histologic Examination.*—The gross specimen was a tumor nodule, about the size of a walnut, circumscribed and firm. In section it did not look unlike a myoma. It consisted essentially of interlacing bundles of highly anaplastic cells and contained numerous mitotic figures and some giant cells. It appeared to be growing rapidly, and in some parts of the section it had invaded the blood vessels. The histologic structure was that of a myosarcoma. This type of tumor is malignant and offers a poor prognosis, the average life of a patient being a little over three years. The tumor tends to produce huge metastases to the liver.

HODGKIN'S DISEASE: A REPORT OF THE POSTMORTEM STUDY OF TWO CASES. ARTHUR W. WRIGHT.

Theories concerning the etiology of Hodgkin's disease are of great interest at the present time. Among the most significant recent studies are those of L'Esperance, who, with Ewing, considers the disease to be a form of tuberculosis probably due to infection with the avian tubercle bacillus, and of Medlar, who believes the disease to be a malignant tumor originating from the megakaryocyte of the bone marrow.

Two cases of Hodgkin's disease which came to necropsy are reported. The first was that of a 14 year old boy who suffered from indigestion, nausea and general weakness and who had a constant though fluctuating fever. The superficial lymph nodes were not palpable, but the spleen was enlarged. Marked anemia and leukopenia were present. Roentgen examination revealed a large mediastinal mass. The condition was diagnosed clinically as miliary tuberculosis. Death occurred about three months after the onset of the disease.

Post mortem there were found: enlarged, matted, markedly necrotic retroperitoneal and mediastinal lymph nodes; marked splenomegaly with suet-like foci of necrosis; a large liver with multiple foci of necrosis, and a hyperplastic bone marrow. The microscopic changes were typical of Hodgkin's disease except for very large foci of acute necrosis of the spleen, liver and lymph nodes and for the presence in all of these organs of abundant phagocytic endothelial leukocytes filled with red blood cells. These cells represent active destruction of blood. So-called Sternberg or Dorothy Reed cells were present in all of the lesions. Fibrosis was only moderate. The bone marrow was extensively involved. No tubercle bacilli could be demonstrated.

The second case, that of a 30 year old colored man, was less acute and was characterized by nausea, indigestion, progressive loss of weight, splenomegaly, ascites, hypertrophy of all the superficial lymph nodes, as well as those of the mediastinum, and fever of the Pel-Ebstein type. Profound progressive anemia and leukopenia were present. In blood films phagocytic cells containing Leishman-Donovan-like bodies were said to have been found, and a clinical diagnosis of kala-azar was made. Death occurred about a year after the onset of the disease.

Necropsy disclosed the characteristic pathologic changes of Hodgkin's disease affecting the spleen, liver, bone marrow and practically every lymph node of the body. Histologically the lesions were older than were those in the first case. Necrosis was less extensive and hyaline fibrosis more marked. There was no evidence of kala-azar. Tubercle bacilli were not found in any of the sections.

These cases, incorrectly diagnosed clinically, are presented to call attention to the importance of adequate and careful clinical and laboratory studies on all obscure chronic diseases with lymphadenopathy, either superficial or mediastinal or both, splenomegaly and fever. Histologically the disease presents the characteristics of an infection rather than those of a malignant tumor.

METASTASIZING LEIOMYOSARCOMA OF THE UTERUS. M. CRISCITIELLO, JR.

A colored woman, 64 years of age, was admitted to the hospital complaining of indefinite abdominal pains and vaginal bleeding. The family history and the past history were of no significance. The patient began to menstruate at the age of 12, and up to the onset of the present illness had had no noteworthy irregularities. She was married at the age of 40, and her husband died ten years later. There were no pregnancies.

About ten years before admission the patient noticed abnormal vaginal bleeding, which manifested itself first in the form of menorrhagia and later metrorrhagia. She paid little attention to these irregularities until four weeks before admission to the hospital, when she bled rather profusely for twelve days. This bleeding was accompanied by slight abdominal pain. After several days of freedom from flow she again began to bleed and had been flowing intermittently until admitted to the hospital. There was a foul odor to the discharge. On admission the patient complained of weakness and loss of appetite.

She was a rather obese colored woman. The chest was normal in contour. The heart showed no enlargement. A loud systolic murmur at the apex, transmitted to the left axilla, and a presystolic murmur, heard best in the second left interspace, were present. The blood pressure was 174 systolic and 80 diastolic. The lungs were resonant except for moist râles over the bases. An irregular, hard, nodular mass filled the lower part of the abdomen. Vaginal examination was unsatisfactory because of the nulliparous outlet. There was slight edema of both ankles.

The red blood cells numbered 2,321,000; the hemoglobin was 35 per cent; the white blood cells numbered 9,200, with 70 per cent polymorphonuclears and 30 per cent lymphocytes. The red cells showed moderate achromia and marked anisocytosis, poikilocytosis and polychromatophilia. The Wassermann reaction of the blood was negative. The urine contained a trace of albumin but no sugar. Much pus was present in the sediment.

A provisional diagnosis of papillary cystadenoma of the ovary or multiple leiomyomas of the uterus was made.

An operation, though necessary, could not be performed because of the poor condition of the patient. Two blood transfusions failed to cause improvement. The patient continued to bleed, and her general condition grew worse. On April 12 she had a profuse hemorrhage following which she died rather suddenly.

At necropsy the most important finding was a large lobulated tumor which filled the lower portion of the abdominal cavity and the pelvis. On removal this mass weighed 4.8 Kg. and was found to consist of the uterus from which sprang multiple smooth, spherical, encapsulated tumors which originated within the myometrium. Most of these tumors were typical leiomyomas. One of them had undergone calcification and could not be cut through. Another, however, was soft and friable, its cut surface resembling brain tissue. This tumor, although partially encapsulated, had broken through the endometrium and had filled the distorted uterine cavity with a soft, spongy, polypoid growth which was necrotic and sloughing. It was obviously malignant.

The ascending colon and several loops of small intestine were adherent to the pelvic mass. The liver, spleen and kidneys showed nothing of note. Throughout

both lungs, especially at the bases, there were many small, roughly spherical tumor masses, varying in diameter from 1 to about 4 or 5 cm. These masses were clearly outlined and white, and on section were found to consist of homogeneous, friable, neoplastic tissue.

The heart was slightly enlarged. In the wall of the right ventricle there was a small metastatic tumor nodule, 1 cm. in diameter. This nodule extended into the right ventricle. Another similar but smaller nodule was enmeshed in the chordae tendineae.

Microscopic examination of the friable, degenerated uterine mass showed atypical, undifferentiated, neoplastic cells which varied morphologically, some being spindle-shaped and others round. Many multinucleated cells and abundant mitotic figures were present. Sections from the pulmonary and myocardial metastases presented the same histologic picture as that of the primary tumor. The tumor was considered to be a rapidly growing leiomyosarcoma of the uterus with metastases to the lungs and the myocardium. The neoplasm apparently originated as the result of malignant transformation of a benign leiomyoma.

PERIARTERITIS NODOSA. V. C. JACOBSEN.

A Negro, 49 years of age, complained of gastric distress and weakness associated with diarrhea, fever and a slow pulse. Physical examination showed midabdominal tenderness, a large heart and sclerosis of the superficial arteries. The Wassermann reaction of the blood was strongly positive. The white cell count varied between 11,000 and 20,000. Diagnoses of acute gastro-enteritis and syphilis were made. The symptoms disappeared shortly, but the fever persisted.

One month later he complained of constant pain in the umbilical region and the loss of 60 pounds (27.2 Kg.) during the preceding three months. The skin was dry and the throat reddened; the cervical, axillary and inguinal glands were enlarged. The white cell count dropped to 9,400. There was a low grade fever.

Five months later he complained of umbilical and retrosternal pain associated with vomiting, dyspnea, weakness and some impairment of vision and hearing on the right side. The hemoglobin was 60 per cent. The white cell count was 5,500. The nonprotein nitrogen content of the blood, which six months previously was normal, now rose to 208 mg. The blood pressure, which was previously slightly elevated, rose to 192 systolic and 140 diastolic. An electrocardiogram showed left axis deviation and complete branch block.

At autopsy the heart was enlarged and the coronary arteries were thick, tortuous and beaded. The beadlike structures occurred along the sides of the arteries and in some instances completely encircled the vessels. These structures varied from 2 to 5 mm. in diameter and were pearly white. They were most numerous along the posterior branches of the right coronary artery.

The kidneys were of normal size, but showed extensive arteriosclerotic changes. Section revealed small, white, beadlike structures, 2 mm. in diameter, along the larger vessels in the medulla. The left testicle showed early infarction with thrombosis of the spermatic artery.

Microscopic study showed all stages of so-called periarteritis nodosa. The early stage was characterized by fragmenting of the muscle cells in the media and their replacement by a fibrinous exudate. There occurred invasion of the media and adventitia by lymphocytes, polymorphonuclear neutrophils and plasma cells. Edema of the perivascular connective tissue was often present.

Other stages showed an invasion of the fibrinous exudate by fibroblasts and young blood vessels which finally resulted in scar formation or hyalinization. The intima in many instances showed endothelial proliferation. The elastica interna and externa became fragmented at the site of the medial lesion.

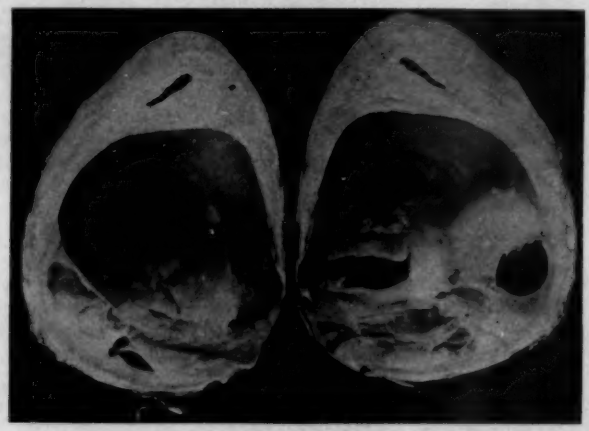
Similar vascular changes were found in the arcuate arteries of the kidneys. A proliferative type of intracapillary glomerulonephritis was present. The spermatic arteries were much affected and often thrombosed. Many other small and medium-sized arteries throughout the body showed the changes described. Additional

lesions were: acute lobar pneumonia, generalized arteriosclerosis, central zone necrosis of the liver, chronic pyelitis, chronic prostatitis and chronic fibrous orchitis.

A Case of Cystic Degeneration of a Large Myoma Simulating Pregnancy. Ellis Kellert.

A woman, aged 45, entered the hospital complaining of vaginal bleeding. The last pregnancy occurred twenty-three years before. There had been one miscarriage. The menses were regular until the onset of the present illness, which began four days before admission with vaginal bleeding associated with pain in the lower part of the back and abdomen. The patient stated that the pains were much like those occurring during labor. No chills, fever or gastro-intestinal disturbances were experienced.

The patient was obese. The only significant physical finding was an enlarged uterus with moderate tenderness in the lower portion of the abdomen. The urine contained red blood cells, but was otherwise normal. The blood count was normal, but there were moderate achromia, anisocytosis and poikilocytosis.



Leiomyoma of the uterus undergoing cystic change. Clinically, the symmetrical enlargement of the uterus simulated a normal pregnancy.

A curettage was performed and greenish fluid obtained, but nothing of diagnostic importance was seen. Several days later the abdomen was opened, and a soft, symmetrically enlarged uterus was found. On palpation no intramural masses were detected. The enlarged organ so closely simulated a pregnant uterus that it was not removed. After this operation an Aschheim-Zondek test for pregnancy was done and found negative.

The patient left the hospital, but the symptoms continued. She returned at the end of three months, and a hysterectomy was performed.

The gross specimen consisted of a uterus with both tubes and the left ovary attached. The uterus measured 12 by 10 by 9 cm. The cervix was not present. The serosa was markedly roughened and injected. The lower half of the uterus was wider and thicker than the fundus, but readily compressible. On section, the uterine wall was represented by a thin layer of smooth muscle within which was a thin layer of myomatous tissue enclosing a cavity, 9 cm. in diameter. This cavity was filled with turbid, greenish-yellow fluid and was divided into several compartments by broad thin bands of myomatous tissue. Masses of fibrin were present in the lower half of the cyst. The endometrial cavity was small and compressed toward the fundus. The endometrium appeared normal. The tubes were not

enlarged or thickened; the serous surfaces were smooth and studded by many minute grayish cysts. The ovary was atrophic.

The fluid from the myoma had a specific gravity of 1.025. No seromucin was present. Smears of the centrifugated sediment showed red blood cells, few leukocytes and no bacteria. Cultures were sterile.

The diagnosis was: a large leiomyoma of the uterus undergoing complete cystic degeneration, hypertrophy of the uterus, glandular hyperplasia of the endometrium and atrophy of the ovary; the fallopian tubes were normal.

AN UNUSUAL POLYP OF THE CERVIX. ELLIS KELLERT.

A woman, aged 56, entered the hospital on May 10, 1931, complaining of bleeding from a tumor mass in the vagina. She had had seven children, five of whom were living and well. There had also been one miscarriage. For many years she had

Large polyp of the cervix which on vaginal examination simulated the fingers of a fetus.

been conscious of a mass in the vagina. Two days before admission she noticed bleeding and conferred with a midwife, who after examination said that she would be all right later. The bleeding became more pronounced, and the patient called a physician. He made a vaginal digital examination and thought that he palpated the fingers of a fetus. She was brought to the hospital and the vagina was examined by means of a speculum. A large cervical polyp was found and removed. It was attached to the left side of the cervix by means of a short narrow pedicle. A smaller polyp was attached to the left side of the cervical canal.

The gross specimen consisted of a skin-covered polypoid mass measuring 7 by 7 by 4 cm. At the narrow end was a cauterized area, 1.5 cm. in diameter. The external surface was thickened, ridged and rough, and had a warty, spinous appearance. Numerous tapering, finger-like projections were attached to the surface. They were about the size of infant fingers and arranged roughly in two rows, one at the larger and broader end of the mass and the other near the narrow attached end. On section, soft, grayish, fibrous tissue was found.

The diagnosis was: a large papilloma or polyp of the cervix having unusual surface configuration and finger-like projections.

A Fatal Case of Argyria. G. H. Klinck, Jr.

At a previous meeting of the society (Klinck, G. H., Jr.: Arch. Path. **15**: 751, 1933), a case of profound argyria was presented in which silver was demonstrated in sections of the skin. A large bladder stone (575 Gm.) from the same patient contained no silver. The patient was discharged after a prolonged convalescence and returned to the hospital two weeks later, very dehydrated. She died in uremia.

Autopsy showed the cutaneous pigmentation previously reported. The heart muscle was atrophic and dark purplish gray, and minute vegetations were present on the mitral valve. Microscopically the stroma showed many silver granules unevenly distributed, often in clumps about small vessels, and a fine deposit rather generalized in the connective tissues. The vegetations contained no silver.

The lungs showed hypostatic pneumonia. Microscopic sections revealed small deposits of silver in the walls of some of the pulmonary veins. The spleen weighed 35 Gm. It showed adhesive capsulitis with silver granules fairly numerous in the thickened capsule but infrequent in the pulp. The liver capsule was grayish. Numerous small foci of necrosis were present. The walls of the veins were gray, owing to heavy deposits of silver granules. The Kupffer cells contained no pigment. The gallbladder contained silver deposits in large amounts in the wall, in nerve trunks, in stroma cells and free in the stroma.

The intestines were dull gray, and the mesentery contained numerous small grayish-black lymph nodes. In the ileum were dark pigment granules in the mucosal phagocytes. The mesenteric nodes contained masses of black pigment.

The kidneys showed marked pyelonephritis. Silver granules were found in the glomerular endothelium. Much pigment of a similar type was present in the cortical tubules along the basement membrane but not definitely in the epithelium itself. The cortical and medullary stroma contained much silver, free and in phagocytes. The pelves, ureters and bladder showed chronic inflammation.

An Unusual Malignant Tumor in the Pelvis of a 14 Year Old Boy. Claude R. Smith.

The patient, a white boy, 14 years of age, was first seen by a physician because of retention of urine. His past history, as given by the family, was that he had been below normal mentally all his life, had suffered from epileptic attacks since infancy, and at irregular intervals during the past year had had periods of acute retention of urine.

The patient was well nourished. The only findings of note were a small tumor mass at the right side of the neck and another in the left inguinal region. A rectal examination was not done. A few days later the tumor of the neck was removed for pathologic examination. A diagnosis of metastatic carcinoma of unknown origin was made.

Six weeks later the boy was admitted to the hospital where a large tumor mass was found in the pelvis. The left inguinal and the cervical lymph nodes were enlarged, and tumor masses the size of a hen's egg were found in the left biceps and in the soft tissues of the left forearm. Roentgen examination of the entire skeleton showed no evidence of tumor invasion of the bone, but there were multiple metastases in the lungs. The patient's condition gradually grew worse as urinary obstruction became more marked. Symptoms of renal damage ensued and the nonprotein nitrogen of the blood rose to 110 mg. per hundred cubic centimeters. There was marked cough with blood-tinged expectoration. The patient became comatose and died two months after he was first seen.

At autopsy the most significant finding was a large tumor mass which almost entirely filled the pelvis. The tumor was situated posterior to the bladder and arose apparently either from the prostate gland or from a seminal vesicle. The

adjacent lymph nodes were infiltrated with tumor, and metastases were found in the lungs, in the myocardium and in the muscles of the left arm. The skeleton was not involved.

Sections from the primary tumor of the pelvis showed a highly anaplastic carcinomatous growth forming in some areas atypical spaces suggestive of seminal vesicle mucosa but not without resemblance to the glands of the prostate. Pathologists differed as to the true origin of the tumor, some thinking that the neoplasm was primary in the prostate gland, and others believing that it arose from a seminal vesicle. Evidence at present is in favor of the second possibility. Such tumors are exceedingly rare.

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## CHICAGO PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, May 8, 1933*

OSCAR T. SCHULTZ, *President pro tempore, in the Chair*

THE CELLULAR INCLUSIONS OF THE SUBMAXILLARY GLAND VIRUS OF GUINEA-PIGS. FLOYD S. MARKHAM and N. PAUL HUDSON.

The intracellular bodies found by Jackson in the enlarged epithelial cells of the ducts of the submaxillary gland of guinea-pigs were shown by Cole and Kuttner some years later to be associated with the presence of a filtrable virus. In sections of tissues which have been fixed in a diluted solution of formaldehyde or Zenker's solution and stained with hematoxylin-eosin or eosin-methylene blue (methyl thionine chloride, U. S. P.) the intranuclear inclusions generally appear as homogeneous or finely granular acidophilic masses. Unstained sections of fixed tissues mounted in glycerin disclose an intranuclear mass which appears to be composed of small round refractile corpuscles of approximately uniform size. Similar sections stained with hematoxylin and decolorized with picric acid also indicate the corpuscular composition of the inclusion.

Fresh unfixed glands taken directly from infected animals and examined in wet mounts have failed to reveal inclusions of the sort seen in fixed and stained preparations. Instead the hypertrophied nuclei of the epithelial cells appear to contain only a few clumps of extremely fine granular material and a few minute refractile granules in active brownian movement. Vesicular structures resembling the enlarged nuclei free from the cell have rarely been seen in such preparations. These vesicles are studded with small corpuscles like those seen in the inclusions of the hematoxylin-picric acid sections. Within the vesicular membrane on which the corpuscles lie are small clumps and refractile granules like those observed in the nuclei of the swollen epithelial cells.

Because of the variation in morphology under these conditions, one should be exceedingly cautious in interpreting the genesis of the inclusion body and its relation to the virus on the basis of fixed and stained materials.

CHRONIC EMBOLIZATION OF THE LUNG. VICTOR LEVINE.

Chronic embolization of the lung, in which multiple emboli are carried to the lungs for a long time, eventually causes marked obstruction of the pulmonary circulation. A 46 year old colored woman had cough and expectoration for ten weeks, pain in the legs for about nine weeks and dyspnea on exertion for three or four weeks. She had marked swelling of the lower extremities, owing to pressure on the veins by a large fibromyomatous uterus. Fifteen hours before death she had a sudden left hemiplegia, followed by marked dyspnea until death.

At autopsy the uterus was firmly wedged in the pelvis, and there were thrombi in the left ovarian, obturator, both iliac, femoral and uterine veins. The right side of the heart was hypertrophied, and the pulmonary artery was occluded by

an embolus which, because of its size, was considered to have come from the inferior vena cava. The large and medium-sized branches of the pulmonary arteries on both sides were occluded by blood clots, which varied from recent, slightly adherent to old, firmly adherent, organized and canalized. These clots were interpreted as multiple emboli from the thrombosed veins, coming to the lungs in showers at different times.

Not all cases of chronic embolization are as clear as this. There may be multiple thrombosis in the pulmonary arteries without any detectable source of possible emboli. Nevertheless, Deschin, Goedel and Ljungdahl consider that in most of these cases there is chronic embolization. Goedel classifies such cases as due to sclerosis of the vessels, arteritis (including syphilis) or chronic embolization. A number of recent cases called examples of thrombosis of the pulmonary arteries appear, on analysis, to be cases of chronic embolization.

In the case now reported the patient lived fifteen hours after the fatal embolism. This long survival is undoubtedly due to well developed collaterals between the pulmonary and bronchial arteries from the gradual occlusion of the pulmonary arteries by multiple emboli.

Thus, chronic embolization must be added to chronic emphysema, pneumonoconiosis, pulmonary arteriolosclerosis, deformities of the spine and congenital or acquired narrowing of the pulmonary veins as a cause of right ventricular hypertrophy.

Cases of chronic embolization are rare. In 1930, Deschin collected sixteen cases and added eight of his own. No previously reported case under this title could be discovered in the English literature.

READJUSTMENT OF THE PULMONARY CIRCULATION IN COMPRESSION THERAPY: STUDIES BY THE INJECTION METHOD. W. R. WILLIAMS.

Since the revival of interest in the surgical treatment of pulmonary tuberculosis, there have been numerous contributions concerning the circulatory changes resulting from pneumothorax, phrenineurectomy and thoracoplasty. A group of investigators headed by Cloetta maintains that there exists an equal circulation in the collapsed lung, while another groups favors the opinion of Bruns that the circulation in the collapsed lung is lessened. An attempt to explain this diversity of opinion would be unsuccessful unless an analysis was made of all the factors concerned, both cardiac and extracardiac. Such an attempt is beyond the scope of this paper, the purpose of which is to deal initially with the mechanical factors.

The materials used for study were the hearts and lungs of thirty-five rabbits, the lungs of three dogs and the lungs of three men. The technic varied slightly according to the information desired. An effort was made to demonstrate the circulation of the lungs in normal expansion, overdistention and various degrees of collapse.

The heart and lungs were removed immediately after the death of the animal. The blood was washed out of the heart and the blood vessels with warm water. Success in the experiment depends largely on the absence of blood clots. A cannula was then inserted into the trachea and tied, and a warm solution of gelatin was injected into the lungs until the desired distention was obtained. The specimen was then placed in cold water and hardened. By this method any degree of distention was maintained. The blood vessels were then given injections of celloidin under continuous pressure for four days, and allowed to harden in water. Then the tissues were corroded with hydrochloric acid and finally washed with running cold water, and the specimen was preserved for study. For the collapse experiment, after washing, the lungs were filled with gelatin to their average normal distention. Then the specimen was placed in warm water. Owing to the elasticity of the lung tissue the gelatin was expressed from the lungs. When the desired degree of collapse had occurred, the specimen was placed in cold water and hardened. When collapse of one lung was desired, a ligature was tied below the bifurcation of the trachea, and the other lung was allowed to collapse. The specimens prepared were a cast of the cavities of the heart, the great vessels,

the blood vessels of the lungs and their branches to include the precapillary area. The bronchial artery was not injected. An attempt was made to imitate the appearance of the vessels in various degrees of distention and collapse.

When the thorax was opened the lungs collapsed. Most of the blood had been compressed out of the smaller blood vessels, and had accumulated in the larger blood vessels and the cavities of the heart. The lungs were about one-third their average normal size. An attempt was made to distend the arterial circulation with water to ascertain the difference in the size of the lungs when the arteries were distended. This proved unsuccessful, however, because the blood vessels ruptured, and the air spaces were distended. That this rupture occurred in the smaller arteries was evident because it did not interfere with subsequent filling with celloidin when the walls of the blood vessels were supported by the gelatin. If this part of the experiment had been successful, some information could have been obtained regarding the resistance offered by the collapsed lung.

Uniform distention of the lungs with gelatin was accomplished easily. The resistance offered to subsequent filling of the blood vessels with celloidin, as measured by the amount of pressure required for successful filling, varied with the solidity of the gelatin. A 3 per cent solution was satisfactory. The specimens most successfully filled were those distended to their normal size. The blood vessels were filled to include, but not exceed, the precapillary area. With overdistention the blood vessels became elongated and narrowed. The greater the distention the less successful was the injection. The smaller arteries were obliterated.

The size of the lungs varied with the degree of collapse; this occurred largely at the expense of the alveoli and bronchioles. In the lesser degrees of collapse the smaller arteries were brought closer together. However, they were filled with celloidin. As compression increased and the lungs continued to decrease in size, increased pressure of the injection fluid compensated for this resistance, but only partially. When the compression had advanced to a stage where there was angulation of the smaller blood vessels, they failed to fill, even with increased pressure. Consequently there was dilatation of the larger branches, and they became tortuous. The dilatation due to increased pressure also affected the contralateral lung. This observation is of interest because of the possible influence on cardiac output.

Another interesting observation was made when the pulmonary veins became filled simultaneously with the arteries. This occurred because of defective closure of the foramen ovale, and was noted in three of thirty-five rabbits. The same was observed in nine of thirty-two human hearts obtained for the purpose of studying the coronary arteries. In none of these patients was the condition recognized during life; none died from cardiac disease. The clinical significance is that while intra-auricular pressure is equal on both sides, there are no functional disturbances, while if for any reason (such as mitral stenosis) there is increased unilateral pressure, blood is interchanged between the auricles.

The pericardium was left intact in all specimens. The hearts were distended in some instances to fill the pericardial sac. In one instance the pericardium was accidentally incised. When the heart was filled with the injected fluid it dilated, and finally, at a pressure of 140 mm. of mercury, the right auricle ruptured. An attempt was made to rupture the heart while the pericardium was intact. Pressure up to 300 mm. of mercury failed to rupture either the heart or the blood vessels.

*Summary.*—Resistance to the pulmonary circulation is increased in proportion to the degree of overdistention or collapse. The increased resistance can be compensated to some extent by increased pressure. With overdistention of the lungs, the blood vessels become elongated, narrowed and obliterated. Compression of the lungs results in tortuosity, angulation and obliteration of the vessels. The blood vessels of the opposite lung are distended. The circulation in the lung varies with, and is dependent on, the degree of overdistention or compression and the functional integrity of the right ventricular myocardium to compensate for the increased resistance.

THECA CELL TUMORS OF THE OVARY. PERRY J. MELNICK.

Two cases of a newly recognized entity, theca cell tumors of the ovary, are reported. Both occurred in women long past their menopause, in whom bleeding began again. In one case the bleeding was periodic, like the normal menstrual cycle. The endometrium in both cases was distinctly hyperplastic, and the uterus large. The tumors were composed of cells which had the histologic characteristics of theca interna cells. Apparently these tumors secreted theelin. This conclusion is supported by much experimental and deductive evidence cited in the literature that the theca cells secrete the estrogenic hormone.

FRIEDLÄNDER'S BACILLUS MENINGITIS SECONDARY TO BILATERAL ACUTE OTITIS MEDIA. G. HOWARD GOWEN.

A woman, aged 63, had influenza in December, 1931, and in the third week of January, 1932, had symptoms which developed into bilateral ruptured otitis media. In May, 1932, an acute right mastoiditis was drained. An abscess appeared in the right posterior triangle of the neck and was drained, but the sinus failed to close. Cultures of the exudate demonstrated Staphylococcus aureus and Friedländer's bacillus. Cerebral symptoms began on August 5, and death occurred on August 12. Postmortem examination demonstrated an acute exudative leptomeningitis, and Friedländer's bacilius was identified culturally.

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## PATHOLOGICAL SOCIETY OF PHILADELPHIA

*Regular Meeting, May 11, 1933*

MORTON MCCUTCHEON, *Vice President, in the Chair*

COMPARATIVE STUDIES ON THE DEFICIENCY DISEASES OF BONE IN MAN AND IN MONKEYS. E. P. CORSON-WHITE, R. S. BROMER and IRVIN STEIN.

Experiments have indicated clearly the importance of calcium and phosphorus in bone formation and also the antagonism between vitamin D and phosphorus on the one hand and parathyroid extract-Collip, calcium, magnesium, strontium and even lead on the other. To a certain extent such experimental work has been hindered by the fact that most of it was done on rats. There is a histologic difference in the rat parathyroid as compared with the human, the former being characterized by the absence of oxyphilic cells. Physiologically, it is difficult if not impossible to produce rickets in the rat if the diet contains a sufficient amount of phosphorus, even though vitamin D is absent. In man it is definitely known that an absence of vitamin D will permit the development of rickets even though phosphorus is present in sufficient amounts, or an excess of phosphorus may easily produce a phosphorus rickets characterized by tetany.

The deficiency diseases of bone in monkeys present much the same roentgen appearance as do those in man. In rickets, the changes as observed in an orangutan aged 13 months were widening of the diaphyseal ends, fraying out of the zone of temporary calcification, haziness of outline of the epiphyseal centers and generalized decalcification of the diaphyses as shown by a streaked appearance of the cortex. In osteomalacia extreme thinning of the cortex, generalized decalcification and multiple fractures of the shaft were usually found. In osteitis fibrosa cystica widening of the ends of the shafts due to bone cysts and giant cell tumors, together with marked thinning of the cortex, generalized decalcification and occasionally increased trabecular shadows, were noted. In Paget's disease, the appearance is that of osteomalacia, except that increased density of the cortex occurred in scattered areas with increased porosity of bone in others. The tables

of the skull were thickened as in man, with scattered areas of decreased density and decalcification. No case of osteoporosis circumscripta or localized Paget's disease was found in the live monkeys and museum specimens examined.

Metabolic studies of these conditions in both man and monkeys yielded similar results. Rickets could not be compared, as it has been impossible to obtain monkeys sufficiently young for such work. Most authorities consider osteomalacia as an adult rickets. The researches of Miles and Chih Tung on osteomalacic women and our studies of seven osteomalacic monkeys showed a constant definite loss of calcium and a retention of phosphorus, magnesium and sulphur together with a lowered serum calcium and phosphorus content. In osteitis fibrosa cystica there was a marked loss of calcium and phosphorus in the urine and feces and a high serum calcium content associated with a low value for serum phosphorus. One monkey with this condition was studied and gave the same results. In Paget's disease the metabolic findings in five human subjects and three monkeys were a retention of calcium, phosphorus and magnesium and a constant loss of sulphur. The values for serum calcium and phosphorus in both groups were normal or very close to normal.

These results indicate that for the study of these bone diseases the monkey is more valuable than the rat. The deficiency diseases of bone are considered by us to be similar in man and monkeys.

Work is now in progress on the possible relationship of these diseases and on the evaluation of the parathyroid factor.

TORULOSIS IN MAN, THE CHEETAH AND EXPERIMENTAL ANIMALS. FRED D. WEIDMAN and HERBERT L. RATCLIFFE.

Torulosis of man, i. e., infection by Torula histolytica, is essentially a disease of the central nervous system. Clinically, it most often simulates tuberculous meningitis. Involvement of the brain and cord takes the form of a chronic meningo-encephalitis. Histologically, the membranes are more or less diffusely thickened by fibrosis and an accumulation of large mononuclear cells. This tissue is loosely arranged and contains large numbers of free and phagocytosed yeast cells. Within the brain the cortical tissues and basal ganglions are usually involved by varying numbers of small, single or multilocular cysts disposed around vessels. These contain a jelly-like substance which, in section, is made up of masses of yeast cells proliferating and expanding without any important reaction on the part of the surrounding tissue.

A case of torulosis was discovered in a cheetah, or hunting leopard, Cynaelurus jubatus, dying in the Philadelphia Zoological Garden. The animal showed a much more generalized infection than is usual for man, indeed probably the most extensive on record. The lesions consisted of a chronic cystic meningo-encephalitis, massive diffuse involvement of the spleen, kidneys and retroperitoneal lymph nodes and miliary foci in the liver, lungs, mesenteric lymph nodes, suprarenals and pancreas. The reaction in the central nervous system was similar to that in man. The spleen was hugely enlarged and may be described as simply an encapsulated mass of yeast cells, necrotic débris and mononuclear leukocytes with but scattered remnants of splenic tissue. Hemorrhages were numerous. The kidneys contained large numbers of small granulomas, and much of the intervening tissue was densely infiltrated by lymphocytes and plasma cells. The granulomas were made up of proliferating fibrous tissue which was infiltrated by monocytes. Free and phagocytosed yeast cells were numerous in these areas. Colonies of yeast cells were also found in glomeruli and tubules, unaccompanied by inflammatory response. All of the lesions within the liver, lungs, pancreas, mesenteric lymph nodes and suprarenals were of microscopic size and made up of monocytes and giant cells which replaced the normal tissues and had phagocytosed many of the yeast cells. The parasites were also present in spaces between the inflammatory cells and occasionally within blood vessels that remained in the lesion.

Cultures were not attempted from the cheetah, but twenty strains of T. histolytica were injected intrameningeally into five cats and twenty-eight white rats. Lesions did not develop in the cats. In the rats there were nine instances of generalization (lungs, spleen, liver, kidney and pancreas) besides involvement of the brain and spinal cord. In no case were cysts recognizable grossly, probably because the lesions did not have time to develop fully. Microscopically, however, both the torular and tissue reactive changes were similar to those in man. In a monkey, inoculated subcutaneously, frank and permanent lesions developed locally, but without generalization.

The outstanding points of the presentation were the observations on the cheetah: (1) the occurrence in a wild animal, though in captivity (only one other case has been reported in an animal, a horse); (2) the widespread generalization with massive involvement of the spleen and kidneys; (3) the remarkably thick, apparently mucinoid envelop around the parasites; (4) the extremely wide range of type of tissue reaction, and yet (5) no participation by leukocytes; (6) a negligible reaction in the brain tissue even in the presence of large cysts crowded with parasites, and (7) the absence of polymorphonuclears.

AGRANULOCYTOSIS AND ACUTE LEUKEMIA. MAX M. STRUMIA.

1. Evidence gathered from the clinical course, the hematologic picture and the anatomic lesions occurring in agranulocytosis and acute leukemia points to many similarities between the two conditions. These are made more convincing by at least six cases of transition of one form into the other, three of them being presented in this paper, one with recovery. The essential lesion which dominates both pictures seems to be a disturbance of the bone marrow, when the mature and undifferentiated parent cells become incapable of maturation. This lesion is very likely based on a constitutional imperfection of the hematopoietic system, congenital or acquired. The rôle played by intercurrent infections, toxemias or susceptibility to various substances is probably a deciding, but not necessarily a specific, factor. An essential difference between the two forms seems to be in the mechanism of release of the immature and undifferentiated cells in the circulating blood, a release which occurs in acute leukemia but not in agranulocytosis.

2. On the basis of theoretical considerations regarding the normal maturation of granulocytic cells, suspensions of normal leukocytes from the human blood have been employed in the treatment of neutropenia. Definite evidence has been gathered that the injection of a leukocytic suspension intramuscularly greatly stimulates the maturation of granulocytic cells. So far, ten patients with agranulocytosis have been treated, and all recovered. In nine of them the favorable effect of the leukocytic suspension appears to be unquestionable. Concerning the tenth patient, the conclusion is doubtful, because of the numerous other therapeutic measures employed and because of the insufficient hematologic data available at the present time.

The stimulating effect of intramuscular injections of a leukocytic suspension has also been demonstrated in neutropenia of other types (acute leukemia, severe infection and malignant tumor).

A SIMPLIFIED ACETONE-GIEMSA STAINING METHOD FOR BLOOD SMEARS. JOHN EIMAN.

This method is recommended for use in routine blood counts. It gives a picture practically similar to that obtained by the acetone-Giemsa method but is much more simple in application and considerably less expensive. The steps of the method are: (1) Fix the blood smears in methyl alcohol for from three to five minutes; (2) immerse the slides for ten minutes in a Coplin jar containing the acetone-Giemsa stain diluted with distilled water 1:10 (this dilution is good for about twelve hours); (3) dry the smear without washing.

The acetone-Giemsa stain is prepared by mixing equal parts of Grübler-Giemsa's solution with chemically pure acetone. The reaction with the distilled water is of

utmost importance. If the water is too acid, the film of blood is going to be rather bright pink, and granules of neutrophils will be eosinophilic. If the water is too alkaline, the smear will have a bluish-green appearance, and neutrophilic granules will be dark bluish. When the reaction of the water is right, the smear will have a slightly bluish-green tint in the thicker portions, neutrophilic granules will be truly neutrophilic, and the platelets will have a pale purplish appearance. To correct the reaction usually the addition of either a drop of a 1 per cent solution of sodium carbonate or a drop of 0.5 per cent glacial acetic acid to 1,000 cc. of distilled water is sufficient. Attempts to buffer the water and to adjust it to the desirable $p_H$ have not been successful.

# Book Reviews

**The Biology of the Protozoa.** By Gary N. Calkins, Ph.D., Sc.D., Professor of Protozoology, Columbia University, New York. Second edition, thoroughly revised. Cloth. Price, $7.50, net. Pp. 607, with 223 engravings and 2 colored plates. Philadelphia: Lea & Febiger, 1933.

This work does not attempt a comprehensive account of protozoology, but is a study of biology as represented by the protozoa. The author attempts to present "the concept of a changing organization brought about by continued metabolism" and to use it for the interpretation of life cycles, reproduction, maturation and senescence. A brief section on parasitism and disease is added in this edition in recognition of the fact that they should be included in any consideration of general biology.

The volume contains fourteen chapters. Chapter I forms an introduction and deals with the size, form and appearance of protozoa. The fundamental organization is given in chapter II, and the derived organization in chapers III and IV. A general account of physiology forms chapter V. Chapters VI, VII, VIII and IX comprise a closely integrated series dealing with methods of reproduction, vitality, phenomena accompanying fertilization, effects of reorganization and the origin of variations in the protozoa. Chapter X deals with general ecology, commensalism and parasitism. The last four chapters (XI, XII, XIII and XIV) comprise special morphologic and toxonomic considerations of Mastigophora, Sarcodina, Infusoria and Sporozoa.

Throughout the author is to be congratulated on his physiologic point of view and his stress of experimental methods. Although he has accumulated a mass of data, most of it has been carefully digested and arranged in a logical treatment in which his own views are repeatedly manifest. This is nowhere better shown than in his treatment of the questions of vitality, reorganization and rejuvenescence, a field in which Professor Calkins' views are of particular interest to protozoologists because of his many contributions to it. In brief, he believes, as suggested by Child, that "senescence consists in a decrease in metabolic rate determined by the change in, and the progressive accumulation of, the relatively stable components of the protoplasmic substratum during growth, development and differentiation." In some protozoa, such as the animal flagellates in which fertilization processes are unknown, it seems probable that the reorganization after each cell division is accompanied by sufficient rejuvenescence to overcome these progressive senescent changes and to allow indefinite asexual reproduction. In other cases (notably the ciliates) in which cell division does not leave the cell in its original labile condition, a progressive aging occurs as asexual reproduction proceeds so that such a line gradually becomes senescent and eventually dies out unless the reorganization and the concomitant rejuvenescence of endomixis or conjugation intervene. In these forms there is essentially the natural death after a typical life cycle as originally postulated by Maupas. Although he disagrees with Woodruff's contention that the loss of vitality is not due to intrinsic aging but to insufficient culture methods, he does stress the changes in the life cycle due to environmental stimuli. As he aptly states in the preface, if the self-regulating mechanisms of reorganization are recognized the protozoa are potentially immortal in the sense of Weismann, but not each a potential germ cell as postulated by Weismann.

Pathologists and parasitologists will be particularly interested in chapter X in which the protozoa are divided into six ecologic groups: those that are water-dwelling, semiterrestrial, soil dwelling, sapropelic, coprozoic and parasitic. The major part of the chapter deals with the parasites. Although the specialist might question some of the specific statements, the descriptions of the groups are in general excellent, but necessarily limited. Nor will the

specialist find a general technical account of the parasites, but the entire book is recommended to all such workers as a biologic survey which places the parasitic protozoa in their proper relationship to the free-living forms and treats them as a special ecologic group. This is of particular importance because there has always been a tendency for the parasitologist to consider parasites as things apart about which to build special philosophical systems, forgetting that the main generalizations should apply primarily to free-living forms and secondarily to the specialized parasites.

The entire book is beautifully illustrated to a large extent with drawings by the author. There are a compact bibliography covering eighteen pages and a complete index.

**La spécificité biologique. Anaphylaxie, immunité, hérédité.** By M. Martiny, H. Prétet and A. Berné. Price, 35 francs. Pp. 209. Paris: Masson & Cie, 1932.

One of the chapters of the book is preceded by a phrase of Pasteur: "Imagination should lend wings to the thought." That phrase and a statement in the introduction that it is the wish of the authors that the ideas expressed in the book be considered merely as a working hypothesis and as a starting point for further experimentation must be kept in mind when one evaluates the contents of the book. The burden of proof is passed on to future experimental investigators. Having accepted such premise, the critical reader can follow the authors through a discussion of some basic principles of immunology.

A. Berné, a physical chemist, is responsible for the chapters dealing with physics and chemistry. The central idea of the work is the conception that the antibody is a modified antigen. The authors profess the unitary conception of the antibodies. A. Berné has developed a hypothesis of his own on the structure of the atom. The other two authors have applied it, as well as some of his other ideas, toward the elaboration and substantiation of the hypothesis on the origin of the antibody. The essential change occurring in the antigen after its introduction into the animal body is the depolymerization of its molecule, during which process the high dilution in the body fluids is a prime, though not the only, factor. The diluted antigen attaches itself to the globulin of the serum. The diluted, depolymerized, antigenic molecule has a certain characteristic vibratory frequency which is different from the frequency of the subsequently freshly introduced antigen. The two substances, though chemically identical, are like two identical, but differently tuned musical instruments. The frequencies, while different, are harmonious, and as a result of resonance the molecules of the antigen combine by polymerization and thus increase in size. After a certain maximum size is reached, flocculation occurs. In that process the antibody plays the rôle of an autocatalyzer. Great emphasis is laid on the very high dilutions of the antigen, and, therefore, in the theoretical and in the experimental chapters infinitesimal quantities are employed. In this and in other respects the homeopathic inclinations of the authors are evident.

The first chapter of the book, which covers the history of the concept of biologic specificity, is followed by seven chapters dealing with newer developments in certain fields of physics, with the physical chemistry of antigens, with specific antibodies, with the antigen-antibody reaction, with anaphylaxis and hypersensitiveness, with immunity in infectious diseases, with heredity and with biologic and therapeutic individuality. Nineteen pages of the appendix give highly theoretical, physical and chemical considerations, heavily loaded with higher mathematics, and the final fifteen pages are a record of the experimental work which was done in an attempt to solve the following problem: If the antibody is a diluted and depolymerized antigen, then it ought to be possible, for instance, to neutralize diphtheria toxin with proper dilutions of the same toxin in vitro or in vivo, or in both ways. No support whatsoever was supplied by any of the

numerous experiments. More successful was the attempt to produce anaphylaxis in guinea-pigs by sensitizing them with infinitesimal quantities of egg albumin. They received by mouth quantities varying from 5 cc. of a 1 : 1,000,000,000 dilution to 5 cc. of a 1 : 1,000,000,000,000 dilution. When the guinea-pigs were given other injections intracardially of 0.5 cc. of a 1 : 100 dilution of egg albumin after intervals varying from one to forty-eight hours, they showed unmistakable signs of moderate to marked anaphylactic reactions. Similar results were obtained in animals prepared with subcutaneous injections. The sensitization was of a transient nature and was not uniform. Many animals failed to react.

The book ends with an expression of hope that experimental evidence will be forthcoming. The book is interesting, stimulating and well written.

**Histopathology of the Peripheral and Central Nervous Systems.** By George B. Hassin, M.D., Professor of Neurology, University of Illinois College of Medicine; Attending Neurologist, Cook County Hospital, Chicago. Price, $5.50. Pp. 491, with 229 figures. Baltimore: William Wood & Company, 1933.

"Though neuropathology is essential to an understanding of clinical phenomena, it is given rather inadequate space in ordinary clinical manuals on neuro-psychiatry. To fill the gap, I have prepared the present volume. It embodies largely the results of twenty years' work in the field of histopathology of the nervous system. Diseases of the peripheral nerves, spinal cord and brain are described individually, from a histopathologic angle only, as they are in textbooks on clinical neurology. The frequent references to the clinical aspects of the subject have purposely been made very brief." This statement in the author's preface describes accurately the scope, the general character and the purpose of this latest American book dealing with the structural changes in the nervous system. The title of the book is accurately descriptive. Knowledge of the microscopic structure of normal nerve tissues, even as revealed by the newer methods of study, is taken for granted, and the author plunges at once into the description of morbid nerve structures. The book is divided into four parts: diseases of the peripheral nerves and muscles, diseases of the spinal cord, diseases of the brain, and staining methods. The 229 figures, mostly original, nearly all photographic, illustrate well the morphologic descriptions of the text. One misses a really good illustration of gitter cells, of which there is much talk in the book. At the end of each chapter is a list of helpful references to the recent literature of the subject discussed. A few questions and comments, largely of minor nature, suggest themselves. Is not epidemic poliomyelitis a much more commonly used name nowadays than either acute anterior poliomyelitis or Heine-Medin's disease? Why include certain forms of tuberculosis and other granulomatous diseases under tumors in the case of the spinal cord and not in the case of the brain? Why include them under tumors in any case? To the student such inclusion cannot but be confusing. And why long, separate descriptions under inflammation of so-called "carcinomatous meningitis and pachymeningitis?" By the way, the description and naming of gliomas are fully up-to-date. Trichinosis encephalitis and trichiniasis encephalitis and like combinations should be avoided. The cerebrospinal fluid does not receive any consideration. The statement on page 442 that botulism is "poisoning with decayed meat" needs correction. In the index, which should have been made more elaborate, rabies is listed only under encephalitis. The presentation is orderly, systematic and comprehensive. The descriptions of the microscopic appearances are accurate and thorough, but the language is not always simple and clear. At times the description becomes almost more detailed and minute than necessary. The learned and conscientious author has spared no pains to explain fully the complicated microscopic structural basis of diseases of the nervous system as now understood, and there is no question concerning his complete mastery of the subject. Hassin's book, at the moment, stands as a leader in its field, and it will be of great help to all who are interested in the microscopic morphology of nervous diseases.

**Die Histopathologie der Uterusmucosa. Ein Leitfaden für Gynäkologen and Pathologen bei der histologischen Diagnostik.** By Dr. H. T. Deelman, Ord. Prof. der allgemeinen Pathologie und pathologischen Anatomie der Reichsuniversität Groningen. Paper. Price, 22 marks. Pp. 247, with 248 illustrations. Leipzig: Georg Thieme, 1933.

This book is written as a guide to the microscopic diagnosis of the endometrium. It is the product of the thorough study for ten years of material submitted to the author by his gynecological colleagues. There are eight chapters. The first deals with the endometrium in pregnancy, uterine and extra-uterine. The various normal and abnormal changes that may occur in the endometrium in connection with pregnancy are described and illustrated. The second chapter is devoted to hydatid mole and choriocarcinoma. About thirty-three figures illustrate the appearances described in this chapter. Chapter three presents the microscopic appearances in endometritis, including the tuberculous form. In the fourth chapter the author describes various atypical conditions in the uterine mucous membrane due to vital as well as to traumatic influences. Then there is a chapter on uterine polyps and other nonmalignant tumors of the endometrium. The sixth chapter is occupied with carcinoma of the uterus and its microscopic diagnosis. Nearly fifty figures are used to elucidate the descriptions. Epidermoid and other carcinomas of the cervix are not considered. The seventh chapter is concerned with endometrial hyperplasia and the effects of the menstrual cycle on the endometrium. The relations of endometrial hyperplasia to hormonal influences are considered. The final chapter describes the uterine mucosa in the climacteric. The presentation is based almost entirely on material obtained from individual cases, which are described briefly. The excellent illustrations, all original photomicrographs, reproduce appearances observed in the microscopic study of this material. Consequently there is the closest possible relation between the text and the illustrations. All who are actively concerned in the microscopic examination of the endometrium for diagnostic purposes will welcome this book warmly. It is a modern and highly efficient guide in its field.

**Lymphatics, Lymph and Tissue Fluid.** By Cecil K. Drinker, B.S., M.D., Professor of Physiology, Harvard School of Public Health, and Madeleine E. Field, A.B., Ph.D., Instructor of Physiology, Harvard School of Public Health. Price, $3. Pp. 254. Baltimore: Williams & Wilkins Company, 1933.

This is a clear, concise and therefore readable and authentic volume on the known and the probable in the matter of lymph, lymphatics and the production of lymph in health and in disease. The volume is the outcome of the senior author's interest and work on certain phases of the problem of lymph for a number of years. The eight chapters deal with the histogenesis and structure of the lymphatic system; the entrance of foreign matter and colloidal solutions into the lymphatics; the permeability of the blood capillaries and its bearing on the production of lymph; the mechanics of the flow of lymph; the chemical composition of lymph and tissue fluids; assays on lymph in circulatory edema, in hypertension, under conditions of lowered plasma proteins, asphyxia, anaphylactic shock and inflammation, and as affected by heat and light. Investigators in the fields of normal and pathologic physiology, surgery, internal medicine and physical therapy will find the monograph a storehouse of information, keen analysis and clear discussions.

# Books Received

STUDIES FROM THE INSTITUTE FOR MEDICAL RESEARCH, FEDERATED MALAY STATES, No. 21, KUALA LUMPUR: MELIOIDOSIS. A. T. Stanton, C.M.G., M.D., F.R.C.P., Chief Medical Adviser to the Secretary of State for the Colonies; formerly Director of Government Laboratories, F.M.S.; and William Fletcher, M.D., M.R.C.P., Member, Colonial Advisory Medical Committee; formerly Director, Institute for Medical Research, F.M.S. Pp. 59, with 37 figures. London: John Bale Sons & Danielsson, Ltd., 1932.

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